Unfavourable Curves: Sex-Specific Lipid Metabolism and Lifelong Cardiovascular Risk

Abstract

Background: Dysregulated lipid metabolism, particularly elevated low-density lipoprotein cholesterol (LDL-C), is a major driver of atherosclerosis as a subset of cardiovascular disease (CVD). Sex differences in lipid biology and the cumulative burden of LDL-C influence disease onset and severity, yet clinical practice often relies on single time-point measurements.

Methods: This review synthesizes evidence from epidemiological, genetic, and mechanistic studies exploring lipid metabolism, sex-specific risk, cumulative LDL-C exposure, and the efficacy of pharmacologic and interventional therapies. Key studies of familial hypercholesterolemia (FH), longitudinal LDL-C trajectories, and major clinical trials of statins, ezetimibe, PCSK9 inhibitors, hormone replacement therapy (HRT), and lipoprotein apheresis were examined.

Results: Lifelong elevated LDL-C significantly increases CVD risk, with Mendelian-randomization analyses indicating that early reductions confer a 3-fold greater benefit per unit LDL-C than interventions started later in life. Men display higher early-life LDL-C and earlier onset of CVD, whereas premenopausal women benefit from estrogen-mediated lipid regulation, which diminishes post-menopause. Statins, particularly when initiated early, effectively lower LDL-C and reduce surrogate markers of atherosclerosis; combination therapy with ezetimibe or PCSK9 inhibitors provides additive benefits. HRT improves lipid profiles but carries cardiovascular and oncologic risks, limiting routine use. Lipoprotein apheresis offers substantial LDL-C and Lp(a) reduction in severe FH.

Conclusions: Both the magnitude and duration of LDL-C exposure are critical determinants of CVD risk. Early and sustained intervention tailored to sex and individual risk optimizes prevention and management. Future research should address longitudinal lipid trajectories, sex-specific responses to therapy, and integration of cumulative lipid metrics into clinical practice.

1. Introduction

The cardiovascular system sustains human life by maintaining the continuous circulation of oxygenated blood, nutrients, and metabolic substrates essential to systemic homeostasis; as a result, its failure—even transiently—carries severe physiological consequences (Chaudhry et al., 2022). Cardiovascular disease (CVD) encompasses a spectrum of disorders affecting the heart and its vasculature, most prominently coronary artery disease, cerebrovascular disease, and heart failure, and remains the leading global cause of death, accounting for approximately 17.9 million deaths annually or nearly one-third of all global mortality (Lopez et al., 2023; World Health Organization, 2019; Benjamin et al., 2018). It also constitutes an immense economic burden, generating an estimated $237 billion in indirect annual costs and is projected to exceed $368 billion by 2035 (Dunbar et al., 2018). Although the past half-century has seen remarkable advances in diagnostic imaging, pharmacological therapy, and surgical intervention that have improved acute outcomes, the overall prevalence of CVD continues to climb due to factors such as population aging, lifestyle-related risk factors, and widening

health disparities (Zhou et al., 2022). The persistence of this burden thus highlights the need to interrogate the biological determinants that shape cardiovascular risk across the lifespan.

Among these determinants, dysregulation of lipid metabolism has long been recognized as central to the pathogenesis of atherosclerotic disease (Steinbeck et al., 2025). Atherosclerosis—characterized by the accumulation of lipid-rich plaques within the arterial wall—develops gradually over decades and underlies most ischemic cardiovascular events (Pahwa & Jialal, 2023). While the cellular and molecular mechanisms governing plaque initiation and progression have been well-characterized, with endothelial dysfunction, oxidative modification of low-density lipoprotein cholesterol (LDL-C) and chronic vascular inflammation primary among them, these processes remain influenced by systemic metabolic and hormonal states (Popa-Fotea et al., 2023). Consequently, lipid metabolism serves as both a mechanistic and epidemiological bridge between molecular pathophysiology and population-level disease risk.

The risk of CVD demonstrates marked demographic heterogeneity. Men generally exhibit a higher incidence at younger ages, whereas the risk for women increases sharply following the onset of menopause, narrowing the sex gap in later decades (Merz & Cheng, 2016). The mechanistic basis of this disparity remains incompletely understood, though converging evidence implicates differences in lipid metabolism as a major driver (Robinson et al., 2022). Estrogen exerts multiple cardioprotective effects, including enhanced hepatic clearance of LDL-C and increased high-density lipoprotein cholesterol (HDL-C) levels, which mediate reverse cholesterol transport (Palmisano et al., 2017). The decline in circulating estrogen after menopause attenuates these protective mechanisms, contributing to unfavourable shifts in lipid profiles and narrowing the sex gap in CVD risk during later adulthood (Raj et al., 2023). By contrast, men, lacking this hormonal modulation, exhibit elevated LDL-C and reduced HDL-C levels throughout life, consistent with their earlier disease onset (Pérez-López et al., 2010).

Despite the well-established association between serum cholesterol and CVD, the relationship between lipid metabolism, sex, and aging remains incompletely defined. Much of the epidemiological literature has emphasized static lipid measurements rather than the cumulative exposure to atherogenic lipoproteins over time—a factor that may more accurately capture lifelong cardiovascular risk (Zhang et al., 2021). Moreover, sex-specific variations in hormonal milieu, hepatic lipid regulation, and lipoprotein turnover complicate traditional interpretations of cholesterol as a uniform biomarker (Seidemann et al., 2024). These considerations have prompted the examination of cholesterol as a dynamic indicator of metabolic aging and hormonal influence.

Consequently, this literature review synthesizes current evidence on cholesterol as a risk factor for CVD and sex differences in lipid profiles to examine cholesterol levels relative to age as a proxy for cumulative lipid burden across the lifespan. We examine whether this index exhibits sex-specific associations with CVD risk and whether cumulative lipid exposure, mediated by hormonal and metabolic factors, partially explains the demographic patterns observed in disease incidence. By integrating mechanistic insights with epidemiological data, this review aims to clarify how cumulative lipid burden and hormonal regulation jointly shape the pathophysiology of CVD, and to identify critical gaps in understanding that impede the knowledge of sex-specific preventive and therapeutic strategies.

2. Methods

Literature search strategy

A structured literature search was conducted to identify peer-reviewed studies examining the relationship between lipid metabolism, cholesterol regulation, sex differences, and CVD. The primary database used was PubMed, with supplementary searches performed in Scopus and Google Scholar to ensure comprehensive coverage of both biomedical and biochemical research. The search encompassed publications available in English up to October 2025.

Search terms included, but were not limited to, combinations of the following keywords and Boolean operators: “cardiovascular disease” OR “atherosclerosis” AND “cholesterol” OR “lipids” OR “lipid metabolism” AND “sex differences” OR “gender differences” OR “menopause” OR “estrogen”. Additional terms such as “hormonal regulation”, “LDL-C”, “HDL-C”, “reverse cholesterol transport”, and “cumulative lipid burden” were incorporated in secondary searches to refine topic specificity. Reference lists of major reviews and landmark cohort studies were also manually screened to capture relevant primary research not indexed under these search terms.

Inclusion and exclusion criteria

Eligible studies included the following: recent review articles (cutoff: within the past 50 years) providing comprehensive analyses of lipid metabolism in CVD; large-scale epidemiological or cohort studies that examined serum lipid levels, aging, and cardiovascular outcomes in male and female populations; and mechanistic or biochemical studies clarifying the molecular pathways by which sex hormones, particularly estrogen, influence lipoprotein metabolism and atherogenesis.

Exclusion criteria comprised non-peer-reviewed sources, case reports, animal studies without translational relevance, and studies focusing exclusively on unrelated metabolic disorders unless directly connected to cardiovascular lipid metabolism.

3. Results

Collectively, lipid biology is both a causal and modulatory factor in cardiovascular disease. Understanding how lipids circulate, modify, and accumulate within arterial walls is essential to contextualize both epidemiological trends and sex-based disparities in disease burden. Beyond the absolute concentrations of circulating lipoproteins, the cumulative exposure to atherogenic lipids over the lifespan is a central determinant of disease trajectory. This passage provides the biochemical context for understanding sex- and age-related heterogeneity in cardiovascular risk, which will be explored in greater depth in subsequent sections.

Pathology and lipid metabolism

Lipid metabolism is central to the etiology of CVD, primarily through its influence on atherosclerotic plaque formation and progression. Atherosclerosis, the predominant pathological substrate underlying most ischemic cardiovascular events, is a progressive process initiated by endothelial dysfunction, in which the vascular endothelium loses its ability to regulate vascular tone and maintain barrier integrity (Park & Park, 2015). This impairment facilitates the subendothelial retention of apolipoprotein B-containing lipoproteins, primarily low-density lipoprotein cholesterol (LDL-C), which represents the principal atherogenic lipoprotein species (Tabas et al., 2007).

Upon infiltration into the arterial intima, LDL particles undergo oxidative and enzymatic modifications, producing oxidized LDL (oxLDL) (Jiang et al., 2022). OxLDL has multiple atherogenic properties, including upregulation of endothelial cell adhesion molecules, recruitment of circulating monocytes, and induction of

pro-inflammatory signaling cascades (Poznyak et al., 2021). Monocytes differentiate into macrophages within the intima, engulfing oxLDL via scavenger receptors, and as lipid accumulation exceeds cellular processing capacity, macrophages transform into foam cells and form the fatty streak—the earliest visible lesion of atherosclerosis (Chistiakov et al., 2016; Ouyang et al., 2023).

Over time, smooth muscle cells migrate into the intima and deposit extracellular matrix, creating a fibrous cap over a lipid-rich necrotic core (Harman & Jørgensen, 2019). This plaque can remain stable for years, but oxidative stress and inflammatory activity promote thinning of the fibrous cap, increasing the likelihood of rupture, which subsequently exposes thrombogenic contents to circulating blood and precipitates acute coronary syndromes such as MI (Loftus, 2011). Consequently, atherosclerosis is fundamentally cumulative, with lifetime exposure to atherogenic lipoproteins representing a key determinant of disease severity (Almohtasib et al., 2024).

The interactions between lipid species further modulate atherosclerotic risk. While LDL-C contributes directly to plaque formation, high-density lipoprotein cholesterol (HDL-C) mediates protective mechanisms through reverse cholesterol transport, whereby excess cholesterol is effluxed from peripheral tissues and transported to the liver for excretion (Ouimet et al., 2019).

Sex hormones exert a considerable regulatory effect on lipid metabolism, contributing to observed demographic patterns in CVD incidence (Robinson et al., 2022). Estrogen upregulates hepatic LDL receptor expression, increasing clearance of circulating LDL particles and thereby lowering serum LDL-C (Palmisano et al., 2017). Concurrently, estrogen also increases HDL-C levels, which promotes reverse cholesterol transport (Palmisano et al., 2017). These combined mechanisms confer a premenopausal cardioprotective lipid profile in women (Ryczkowska et al., 2022). Following menopause, declining estrogen levels attenuate these protective mechanisms; LDL-C increases, HDL-C decreases, and women's cardiovascular risk rises sharply (Ryczkowska et al., 2022). By contrast, men lack this hormonal protection throughout life, which may explain their earlier onset of CVD (Rodgers et al., 2019).

Sex-specific lipid profiles

Epidemiological data consistently demonstrate pronounced sex-based differences in both lipid metabolism and cardiovascular risk trajectories. Men generally exhibit higher LDL-C and triglyceride concentrations, coupled with lower HDL-C levels, beginning as early as adolescence (Russo et al., 2015). These differences correlate with earlier onset and greater lifetime incidence of atherosclerotic CVD (Rodgers et al., 2019). In contrast, premenopausal women typically maintain a more favourable lipid profile, characterized by lower LDL-C and elevated HDL-C levels, which correspond to their reduced risk of coronary events prior to menopause (Ryczkowska et al., 2022).

This divergence is largely attributed to the hormonal regulation of hepatic lipid processing. Androgen-dominant metabolic environments in males promote increased hepatic lipase activity, accelerating HDL catabolism and reducing HDL-C concentration (Herbst et al., 2003). Concurrently, reduced LDL receptor density in hepatocytes contributes to slower LDL clearance from the circulation; these features collectively produce an early-life metabolic phenotype conducive to lipid retention and vascular injury (Pirahanchi et al., 2023).

The onset of menopause represents a pivotal inflection point in female lipid physiology. Estrogen—the principal modulator of lipid homeostasis in women—exerts multifaceted effects on lipoprotein mechanisms, upregulating hepatic LDL receptor expression, facilitating LDL particle uptake and degradation, and promoting apolipoprotein A-I (ApoA-I) synthesis, the major protein constituent of HDL (Nii et al., 2016; Palmisano et al.,

2018). Moreover, estrogen stimulates the activity of ATP-binding cassette transporters (ABCA1 and ABCG1) involved in cholesterol efflux, thereby augmenting reverse cholesterol transport (Bao et al., 2023).

As endogenous estrogen production declines during the menopausal transition, these regulatory mechanisms wane, leading to measurable alterations in serum lipid composition (Patel et al., 2025). The extent and timing of these changes have been captured through large-scale prospective cohorts, including the Framingham Offspring Study (FOS) and the Study of Women's Health Across the Nation (SWAN) (Duncan et al., 2019; El Khoudary et al., 2019).

FOS, a longitudinal cohort initiated in 1971 to follow the descendants of the original Framingham Heart Study participants, provides some of the most comprehensive sex-stratified analyses of lipid trajectories and cardiovascular outcomes. Among 3,875 participants (54% women; mean age 48 years) followed between 1979 and 2014, investigators identified five distinct trajectories of total cholesterol (TC), LDL-C, and HDL-C across adulthood (Duncan et al., 2019). Women exhibited marked inflection points in LDL-C and HDL-C levels during midlife, consistent with the perimenopausal transition, where average LDL-C concentrations increased by approximately 10–15%, while HDL-C declined modestly—changes that paralleled reductions in circulating estradiol rather than chronological aging or body mass index (Ryczkowska et al., 2022).

Elevated lipid trajectories were strongly associated with future atherosclerotic cardiovascular disease (ASCVD) and mortality. Participants maintaining LDL-C >155 mg/dL, TC >240 mg/dL, or non-HDL-C >180 mg/dL had over a twofold increase in ASCVD and all-cause mortality risk compared with those maintaining optimal lipid levels (HR_{ASCVD} = 5.09 [95% CI: 1.54–16.85]; HR_{death} = 4.04 [1.84–8.89]) (Duncan et al., 2019). Conversely, persistently low HDL-C (<40 mg/dL) was associated with a nearly 4-fold higher ASCVD risk compared with concentrations >70 mg/dL (Duncan et al., 2019). These findings reinforce the concept of cholesterol-years—that is, cumulative exposure to atherogenic lipoproteins—as a more precise determinant of lifetime cardiovascular risk than any single lipid measurement (Wilkins et al., 2024). From a mechanistic perspective, these observations align with the decline in hepatic LDL receptor expression post-menopause, leading to reduced LDL clearance and prolonged lipoprotein residence time within circulation, thereby increasing the probability of oxidative modification and endothelial retention (P, 2025). FOS thus provides population-scale confirmation of the biochemical mechanisms previously discussed.

Complementing the Framingham data, SWAN—a multi-ethnic, prospective cohort initiated in 1994—has characterized the dynamic lipid changes across the menopausal transition in greater temporal resolution. SWAN followed over 3,000 premenopausal women aged 42-52 from diverse ethnic backgrounds (Caucasian, African-American, Chinese, Japanese, and Hispanic) for over two decades, incorporating both hormonal and metabolic assessments at annual intervals (El Khoudary et al., 2019; Derby et al., 2009). Longitudinal analyses across the menopausal stages revealed that the steepest rise in LDL-C and total cholesterol levels occurred within a two-year window surrounding the final menstrual period (FMP), temporally coinciding with the estradiol nadir (El Khoudary et al., 2021). These changes were most pronounced during early postmenopause, when estrogen depletion accelerates hepatic lipid remodeling (El Khoudary et al., 2021).

Mechanistically, SWAN's metabolic substudy highlighted that declining estrogen levels were associated with increased hepatic lipase activity and reduced ApoA-I concentrations, attenuating HDL particle maturation and impairing reverse cholesterol transport (Woodard et al., 2011). Additionally, small dense LDL particles became increasingly prevalent in the years following menopause, a pattern associated with heightened atherogenic potential due to their greater arterial wall penetrance and oxidative susceptibility (He et al., 2025).

Taken together, the Framingham and SWAN cohorts provide converging evidence that the menopausal transition represents a biologically distinct period of lipid remodeling with direct implications for

cardiovascular risk. Framingham emphasizes the cumulative, long-term impacts of rising LDL-C post-menopause on clinical outcomes, while SWAN delineates the temporal and mechanistic sequence of lipid alterations accompanying hormonal delines; its inclusion of diverse populations underscores that, while hormonal decline is universal, its phenotypic lipid effects are modulated by race, diet, and genetic background.

Beyond circulating estrogen, sex-specific lipid metabolism is modulated by androgens and progesterone. Androgens, which predominate in males, exert multiple pro-atherogenic effects, primarily through hepatic lipid regulation (Xu et al., 2022). Elevated androgens increase hepatic lipase activity, accelerating the catabolism of HDL particles and leading to smaller, less functional HDL that is less effective in reverse cholesterol transport (Kantor et al., 1985). Additionally, androgen exposure favors the production of small, dense LDL particles, which are more susceptible to oxidation, exhibit increased arterial retention, and undergo atherogenic modification (Vekic et al., 2022). These molecular and structural alterations provide a mechanistic basis for the higher prevalence of early-onset cardiovascular disease observed in males.

In contrast, progesterone, a dominant female sex hormone during the luteal phase and pregnancy, influences lipid metabolism in a more nuanced manner. Progesterone modulates HDL functionality by altering particle composition and may affect the distribution of LDL subfractions, though the net cardiovascular impact remains less clearly defined (Corsini et al., 1988). Importantly, these effects are context-dependent, influenced by hormonal milieu, age, and concomitant estrogen exposure. Estrogen receptor signaling, mediated by ERα and ERβ, plays a pivotal role in hepatocyte lipid handling, regulating transcription of key genes including LDL receptor, apolipoprotein A-I, and enzymes involved in cholesterol esterification and bile acid synthesis (Zhu et al., 2018). Additionally, estrogen modulates sterol regulatory element-binding protein (SREBP) pathways, which are central to endogenous cholesterol synthesis and intracellular lipid homeostasis (Sakai & Rawson, 2001). Collectively, these hormonal and intracellular mechanisms underlie the observed divergence in lipid profiles between males and females across the lifespan, contributing to delayed atherosclerotic development in premenopausal women and accelerated risk in men and postmenopausal women.

The effects of sex hormones extend beyond circulating lipoproteins to cellular processes in the vascular wall. Estrogen enhances endothelial nitric oxide synthase (eNOS) activity, promoting vasodilation and reducing oxidative stress, while androgens may favor pro-inflammatory cytokine expression and endothelial dysfunction (MacRitchie et al., 1997). These vascular effects amplify the consequences of sex-specific lipid profiles, reinforcing the higher baseline risk of atherogenesis in males and the protective effect of premenopausal estrogen in females.

In addition to conventional lipid fractions, lipoprotein(a) (Lp(a)) represents a genetically determined, highly atherogenic lipoprotein whose plasma concentration is largely stable throughout life and minimally influenced by diet, exercise, or conventional lipid-lowering therapies (Farzam et al., 2024). Structurally, Lp(a) consists of an LDL-like particle covalently bound to apolipoprotein(a), a glycoprotein homologous to plasminogen, which confers prothrombotic properties in addition to its atherogenic potential (Farzam et al., 2024). Elevated Lp(a) levels have been associated with accelerated coronary artery disease, calcific aortic valve disease, and heightened inflammatory signaling in the vascular endothelium (Wambua et al., 2025).

The clinical impact of Lp(a) appears to differ by sex and hormonal status. In premenopausal women, Lp(a)-related risk is partially mitigated by estrogen-mediated enhancement of LDL receptor expression and lipoprotein clearance (Corral et al., 2024). Postmenopausal women, however, experience a disproportionate increase in atherosclerotic cardiovascular disease (ASCVD) risk when Lp(a) levels are elevated, potentially due to the combined effects of increased LDL-C, loss of estrogen-driven hepatic clearance, and heightened inflammatory susceptibility in the vascular wall (Roeters van Lennep et al., 2023).

When contextualized within the broader framework of lipid biology, these findings reinforce the notion that lifetime exposure to atherogenic lipoproteins—modulated by the hormonal milieu—is a principal determinant of CVD onset and severity. This cumulative exposure framework integrates both male and female trajectories: men experience a steady accrual of risk beginning early in adulthood due to persistently higher LDL-C levels, whereas women's risk accelerates sharply post-menopause as estrogen-mediated lipid regulation deteriorates. Such evidence provides a mechanistic and epidemiological rationale for sex-specific therapeutic approaches, discussed in subsequent sections, emphasizing the potential for early lipid intervention in premenopausal women to mitigate post-menopausal risk acceleration.

Cumulative lipid burden and aging

While acute lipid measurements are standard clinical practice, growing evidence emphasizes that cumulative exposure to atherogenic lipoproteins, rather than isolated LDL-C levels, is the principal determinant of CVD risk (Zheutlin et al., 2025). Prolonged circulation of LDL particles increases the probability of their oxidative modification and subsequent arterial retention, accelerating atherogenesis (Maiolino et al., 2013). Indeed, accumulating epidemiological and genetic evidence supports a *cholesterol-years* model of atherogenesis in which the duration of exposure to atherogenic lipoproteins materially influences lifetime risk of coronary heart disease (CHD) (Zheutlin et al., 2025).

Mendelian-randomization meta-analyses provide strong support for the cholesterol-years paradigm. Ference et al. integrated nonoverlapping data from 312,321 participants across nine polymorphisms affecting LDL-C regulation. Each mmol/L genetically lower LDL-C was associated with a 54.5% reduction in CHD risk (95% CI: 48.8–59.5%), reflecting a ~3-fold greater risk reduction per unit LDL-C than statin therapy initiated later in life ($p = 8.43 \times 10^{-19}$) (Ference et al., 2012). These results demonstrate that early and sustained reductions in LDL-C produce disproportionately larger cardiovascular benefits, supporting the notion that cumulative LDL exposure, rather than cross-sectional levels alone, governs atherosclerotic progression. Conceptually, these observations have been framed as the cholesterol-years or lifelong exposure model: the area under the LDL-C curve across the lifespan appears to predict disease more accurately than a single midlife measurement (Ference et al., 2012).

Complementing genetic findings, Zhang et al. 2021 pooled data from four prospective cohorts (18,288 participants; 56.4% women; mean age 56.4 ± 3.7 years; median follow-up ≈ 16 years) (Zhang et al., 2021). Using cumulative LDL-C, time-weighted average (TWA), and LDL-C slope metrics, the study found that both cumulative LDL-C and TWA LDL-C were independently associated with incident CHD even after adjustment for the most recent midlife LDL-C and traditional CVD risk factors (Zhang et al., 2021). By contrast, the LDL-C slope alone was not significantly associated with CHD after accounting for midlife levels, reinforcing that the area *under the LDL curve* (cumulative burden) rather than transient changes in LDL-C is the critical metric (Zhang et al., 2021). Thus a lifelong lipid exposure model is translationally relevant once mechanistic insights from genetic studies are extended into population-level observations.

Further evidence comes from the Copenhagen General Population Study (CGPS) which enrolled 91,131 individuals between 2003 and 2015, with a mean follow-up of 7.7 years (Mortensen & Nordestgaard, 2020). During this period, 1,515 first myocardial infarctions (MI) and 3,389 atherosclerotic cardiovascular events occurred, where each 1.0 mmol/L increase in LDL-C was associated with a 34% higher risk of MI (HR: 1.34; 95% CI: 1.27–1.41) and a 16% higher risk of ASCVD overall (HR: 1.16; 95% CI: 1.12–1.21) (Mortensen & Nordestgaard, 2020). Notably, risk was amplified in older adults (aged 70–100 years) and in individuals with very high LDL-C (≥5.0 mmol/L), consistent with the notion that both absolute levels and cumulative exposure exacerbate atherosclerotic outcomes (Mortensen & Nordestgaard, 2020).

Complementing these observational studies, population screening for heterozygous familial hypercholesterolemia (FH) demonstrates the extreme consequences of lifelong elevated LDL-C. FH, an autosomal dominant genetic disorder caused by mutations in genes critical for LDL clearance that impair hepatic LDL uptake, is characterized by markedly elevated plasma LDL-C concentrations from birth (Warden et al., 2024). Prevalence estimates range from 1/500 to 1/200 in Northern European populations, yet <1% of affected individuals are diagnosed in most countries (Nordestgaard et al., 2013). Individuals with untreated FH experience up to a 13-fold increased risk of CHD, suggesting that prolonged and substantial elevations in LDL-C from early life dramatically accelerate atherosclerosis (Nordestgaard et al., 2013). FH thus provides an application of the cholesterol-years paradigm: both the magnitude and duration of LDL-C elevation are critical determinants of cardiovascular risk, and the findings reinforce the mechanistic link between lifelong LDL burden and atherosclerotic disease.

Collectively, converging evidence from genetic, longitudinal, and clinical studies emphasizes that cardiovascular risk is not merely a function of LDL-C concentration at a single point in time, but rather of its cumulative exposure across the lifespan. Thus, early and sustained lipid control, rather than reactive prevention in midlife, yields disproportionately greater protection against lifetime cardiovascular risk.

Therapeutic strategies and sex-specific limitations

Given the centrality of cumulative LDL-C exposure in atherosclerosis, therapeutic interventions aim to reduce circulating LDL-C levels, enhance clearance, or modify lipid metabolism to slow plaque progression (Table 1).

Therapy	Mechanism of Action	Key Efficacy Data	Notes
Statins	Inhibit HMG-CoA reductase → ↓ cholesterol synthesis → ↑ hepatic LDL receptors → ↑ LDL-C clearance	Pediatric FH: LDL-C ↓ 32% (29–35%), CIMT regression 0.01 mm, flow-mediated dilation ↑ 2.7%	Primary & secondary prevention; early initiation maximizes benefit; safe in children/adolescents
Ezetimibe	Inhibits NPC1L1 → ↓ intestinal cholesterol absorption → additive LDL-C reduction	LDL-C ↓ ~15–20% when combined with statin IMPROVE-IT: 7-year MACE 32.7% vs 34.7% (ARR 2%, HR 0.936), greater benefit in ≥75 years & diabetics	Adjunct to statin therapy, especially when target LDL-C not achieved with statins alone
PCSK9 inhibitors (Evolocumab, Alirocumab, Inclisiran)	Monoclonal antibodies or siRNA block PCSK9 → prevent LDL receptor degradation → ↑ LDL-C clearance	LDL-C ↓ 50–60% FOURIER: major CV events ↓ 15–20% ODYSSEY: LDL-C ↓ 57%, CV events ↓ 15%, safe & well-tolerated	FH, statin-intolerant, high-risk ASCVD; Inclisiran allows long-acting dosing (every 6 months)
Hormone Replacement	Estrogen ↑ LDL receptors, ↑ HDL formation, ↑ reverse cholesterol	LDL-C ↓ 0.47 mmol/L, total cholesterol ↓ 0.43	Postmenopausal women; used mainly for

Therapy (HRT)	transport (ABCA1/ABCG1)	mmol/L, Lp(a) ↓ 49.46 mmol/L	symptomatic relief; cardiovascular benefits secondary due to risks (VTE, stroke, breast cancer)
Lipoprotein apheresis	Mechanical removal of LDL-C and Lp(a) from plasma	LDL-C & Lp(a) 55–70% per session 2-year CV event reductions: isolated LDL ↑ 54%, isolated Lp(a) ↑ 83%, combined ↑ 83.5%	Severe or treatment-resistant FH; homozygous FH; high Lp(a); resource-intensive but highly effective

Table 1. Summary of major lipid-lowering therapies, mechanisms, and clinical outcomes.

Statins remain the first-line therapy for both primary and secondary prevention of CVD. Mechanistically, statins inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis in hepatocytes (Bansal & Cassagnol, 2023). Reduced intracellular cholesterol triggers upregulation of LDL receptors on the liver surface, promoting the uptake of circulating LDL particles and lowering plasma LDL-C concentrations (Trapani et al., 2012). In children with heterozygous FH, statins have been shown to substantially reduce LDL-C levels and slow progression of atherosclerosis. A systematic review including nine randomized placebo-controlled trials (1,177 participants; median follow-up 24 weeks) found statin therapy reduced mean LDL-C by 32.15% (95% CI: 29.4–34.9%) and produced measurable improvements in brachial artery flow-mediated dilatation (2.7% higher; 95% CI: 0.42–4.98) and carotid intima-media thickness (CIMT) (mean change 0.01 mm lower) relative to placebo, both surrogate markers of atherosclerotic burden (Vuorio et al., 2019). Adverse events, including myopathy and changes in liver enzymes, were rare and comparable to placebo, supporting the safety of early statin initiation in pediatric populations (Vuorio et al., 2019).

Ezetimibe, an adjunct to statins, inhibits the NPC1L1 transporter in the intestinal brush border, reducing absorption of dietary and biliary cholesterol (Davis & Veltri, 2007). When combined with statins, ezetimibe provides additive LDL-C reductions (~15–20%) (Hammersley & Signy, 2017). The landmark IMPROVE-IT trial randomized high-risk post-MI patients with recent acute coronary syndrome to simvastatin 40 mg versus simvastatin 40 mg plus ezetimibe 10 mg daily (median follow-up 6 years) (Cannon et al., 2015). Combination therapy further reduced LDL-C (53.7 mg/dL vs 69.5 mg/dL; $p < 0.001$) and decreased major cardiovascular events at 7 years (absolute risk reduction 2.0%; HR: 0.936; 95% CI: 0.89–0.99) (Cannon et al., 2015). Subgroup analyses indicated greater benefit for patients with diabetes (5.5% absolute risk reduction; HR: 0.86) and for older adults aged ≥75 (HR: 0.80) highlighting ezetimibe's role in high-risk populations where further LDL-C lowering is required (Giugliano et al., 2018; Cannon et al., 2015). Meta-analyses of 27 trials (>21,000 participants) confirm that statin-ezetimibe combination therapy produces superior LDL-C reduction compared to statin monotherapy (mean additional reduction 15.1%) and maintains a favourable safety profile (Morrone et al., 2012).

PCSK9 inhibitors, including monoclonal antibodies evolocumab and alirocumab, preserve LDL receptor availability by preventing PCSK9-mediated receptor degradation, significantly enhancing hepatic LDL-C clearance (Jeswani et al., 2024). Clinical trials demonstrate 50–60% LDL-C reduction in patients with heterozygous FH, and reductions in major cardiovascular events of 15–20% (Tomlinson et al., 2021). For instance, the FOURIER trial reported a 59% LDL-C reduction with evolocumab, resulting in a 15% reduction in cardiovascular events; ODYSSEY Outcomes reported a 57% LDL-C reduction with alirocumab and a 15% reduction in adverse events (Jeswani et al., 2024). Inclisiran, a long-acting siRNA targeting PCSK9, achieves similar LDL-C reductions (>50% for 6 months) with less frequent dosing (Jeswani et al., 2024). These therapies

are generally well-tolerated, with injection site reactions being the most common adverse event (Jeswani et al., 2024).

Hormone replacement therapy (HRT) in postmenopausal women can partially restore premenopausal lipid profiles (Nie et al., 2022). Postmenopausal HRT has lipid-modifying effects by upregulating LDL receptors, enhancing HDL-C formation, and stimulating reverse cholesterol transport via ABCA1/ABCG1 transporters (Nie et al., 2022). A systematic review of 73 studies found that HRT significantly reduced LDL-C by 0.47 mmol/L (95% CI: −0.55 to −0.40), total cholesterol by 0.43 mmol/L, and Lp(a) by 49.46 mg/L relative to placebo (Nie et al., 2022). Moreover, the timing of HRT initiation relative to menopause is critical to its cardiovascular effects. Observational and trial data support a "timing hypothesis," whereby initiation within ten years of menopause may confer modest cardiovascular protection, whereas later initiation may increase risks of stroke or coronary events (Hodis & Mack, 2022). Novel pharmacologic approaches, including selective estrogen receptor modulators (SERMs) and tissue-selective estrogen complexes (TSECs), aim to replicate lipid benefits while minimizing systemic risks, though large-scale cardiovascular outcome data remain limited (Pickar et al., 2018). Integration of these therapies with statins or PCSK9 inhibitors may offer synergistic LDL-C reduction in high-risk postmenopausal women, pending further study. Although HRT improves lipid profiles, its clinical use is constrained by increased risk of venous thromboembolism, stroke, and breast cancer, so it is typically reserved for symptomatic relief, with cardiovascular benefit considered secondary (Hodis & Mack, 2022).

In patients with severe or treatment-resistant dyslipidemia, particularly FH, lipoprotein apheresis provides immediate and potent LDL-C and Lp(a) reduction (Feingold, 2023). A multicenter study by von Dryander et al. demonstrated 55–70% reduction in LDL-C and Lp(a) per session. Corresponding reductions in cardiovascular event rates over two years were 54% for patients with isolated LDL elevation, 83% for elevated Lp(a), and 83.5% for combined LDL-C and Lp(a) elevations (von Dryander et al., 2013). Apheresis is intensive and resource-demanding, but offers a life-saving intervention for patients who cannot achieve lipid targets pharmacologically (Lui et al., 2014).

Limitations and gaps, however, remain in sex-specific and longitudinal assessment. Women remain underrepresented in clinical trials, limiting precise understanding of HRT or statin efficacy across different life stages, particularly during postmenopause (Witting et al., 2022). Longitudinal studies tracking cumulative LDL-C from childhood into adulthood remain scarce, limiting the ability to quantify lifetime exposure and optimize the timing of therapy. Despite these challenges, evidence from RCTs and observational studies consistently demonstrates that aggressive LDL-C reduction, especially when initiated early, significantly decreases the risk of cardiovascular events and mitigates cumulative lipid burden; consequently both magnitude and duration of LDL-C exposure are further confirmed to be central determinants of cardiovascular outcomes.

4. Conclusion

Lipid metabolism is a central determinant of CVD, with cumulative exposure to atherogenic lipoproteins—particularly LDL-C—emerging as a stronger predictor of atherosclerotic burden than isolated midlife measurements. Epidemiological, genetic, and Mendelian-randomization studies consistently demonstrate that lifelong lower LDL-C, whether through inherited variants or early pharmacologic intervention, substantially reduces coronary heart disease risk. Sex-specific differences in lipid profiles, driven primarily by hormonal modulation, contribute to divergent CVD trajectories: men experience earlier elevations in LDL-C and greater early-life risk, whereas premenopausal women benefit from estrogen-mediated cardioprotection, which diminishes after menopause.

Therapeutic interventions, including statins, ezetimibe, PCSK9 inhibitors, HRT, and lipoprotein apheresis, effectively target both the magnitude and duration of LDL-C exposure. Evidence highlights the importance of early initiation—particularly in high-risk populations such as children with FH—to reduce cumulative lipid burden and subsequent atherosclerotic events (van den Bosch et al., 2024). Despite such advancements, underrepresentation of women in clinical trials and limited longitudinal lipid-aging data remain key gaps, highlighting the need for sex-specific strategies and lifelong management approaches. Collectively, these findings emphasize that both the quality and duration of lipid exposure are crucial determinants of CVD risk, informing precision approaches to prevention and therapy.

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EDITOR COMMENTS AND RECOMMENDATION:

The reviewers commend the author for researching a complicated and clinically relevant topic with rigor and clear analytical thinking as well as sophisticated, professional writing. One reviewer recommends minor revisions while the other reviewer recommends major revisions, but both agree that the addition of tables/graphical figures would be helpful for better reader understanding. Furthermore, the second reviewer emphasizes the need to highlight the novelty of this review article and to better identify the gaps in the literature being filled by this work. Both reviewers have additional minor edits for clarity and elaboration which should also be addressed. Given the reviewer feedback, the editor's recommendation is to accept the manuscript following major revisions.

REVIEWER 1:

Reviewer Final Recommendation: Accept with minor revisions

Overall, the paper is well written with a clear goal of synthesizing the literature to highlight cholesterol as a risk factor for cardiovascular disease (CVD) with a focus on sex differences of lipid burden across the lifespan to gain mechanistic understanding of CVD risks and identify gaps in the literature hindering therapeutic advances. The author is very well versed in this topic and describes the pathology, lipid metabolism, and sex-specific lipid profiles with enough detail to set the stage for discussing the cumulative burden across aging and ending with the current sex-specific therapeutic limitations. The author does a fantastic job discussing the literature clearly and concisely with ample detail to clearly define the gaps in the literature that are impeding progression towards a therapeutic to mitigate overall CVD risk. Minor revisions are included below to bolster the manuscript for acceptance:

- In the Methods section, please include the total number of studies screened initially as well as the remaining number of studies included in your literature review after the exclusion criteria to give the reader more situational awareness of how many studies you are synthesizing for this topic.
- For the results section, consider consolidating the smaller paragraphs per section to create a few larger paragraphs that flow logically per section. Consolidation of the smaller paragraphs will aid in streamlining the main takeaways and highlighting the main points per paragraph. One example of a section to streamline and consolidate paragraphs is the "Sex-specific lipid profiles" section as there are 15 mini paragraphs total that may flow better if condensed down to 5-6 larger paragraphs with emphasized main findings.

- Consider adding additional transitional sentences between paragraphs to streamline the main takeaway(s) of the paragraphs in each section after consolidating smaller paragraphs together.
- Consider adding in an additional graphical figure that describes the molecular mechanisms involved in lipid metabolism to aid in understanding potential targets for therapeutic intervention and discrepancies in sex specific outcomes.
- Consider adding in an additional graphical figure that illustrates the sex specific lipid profiles and main sex differences in CVD risk to visually highlight the main sex differences reported in the literature.
- Your conclusion paragraph is clear and concise but would be stronger if you added in additional sentences that discuss additional ways to address the gaps in the literature as well as positing potential therapeutics to address the sex- specific differences in CVD risk. Your second paragraph in your conclusion touches on these elements but can be made stronger with additional detailed examples to address the gaps in the literature (similar to how you wrote the last sentence of the last paragraph in the "Therapeutic strategies and sex-specific limitations" section).

REVIEWER 2:

Final Recommendation: Accept with major revisions

Originality & Significance –

- The concept of cumulative lipid burden over time is not new, and the review acknowledges this well. However, if the goal is to emphasize the importance of assessing lifelong lipid exposure in clinical practice, the manuscript would benefit from incorporating more evidence on how this should be operationalized. In particular, additional studies or frameworks demonstrating practical methods, validated metrics, or clinical tools for evaluating long-term lipid exposure would strengthen the argument and clarify the translational relevance. If there is no data on this, you may consider shifting your review to one that identifies literature gaps and future directions needed in the study. Additionally, more background regarding the gaps/errors in current methods should be discussed to underscore the relevance of the study.
- The intended aims are not achieved using the data presented – more empirical studies that utilize cumulative cholesterol, and report sex-based associations with CV outcomes are necessary.

Clarity & Structure

- Clearly written and easy to follow

- Mechanistically very detailed
- The structure is sound and very professional
- Use of Evidence & Research Methods – Appropriately cited, a diagram of the search process would be helpful
- Engagement with Literature – It is clear that you have examined the literature in great depth and are familiar with this topic, great job.
- Grammar & Language – Clear with minimal grammatical errors

Introduction

- The clinical implications of using cumulative lipid measurements to capture "lifelong cardiovascular risk" should be further clarified. Explain to the reader why assessing cumulative exposure is necessary and what current risk estimates fail to capture—e.g., missed events, misclassification, or underestimation of early-life risk. This will help underscore the significance of the review.
- Please expand on the specific gap in the literature that this review intends to address. The introduction already discusses sex differences extensively, which may give the impression that the topic is well-established. If this review contributes something novel, clarify in detail what it adds to existing research and why it is needed.
- You state that the purpose of this review is to "examine cholesterol levels relative to age as a proxy for cumulative lipid burden," but do not define how "cholesterol relative to age" or the "index" is calculated – please clarify this.
- You also state that you will examine sex-specific associations with the index over time however, there is no data to support this. Consider studies that examine this "index" by sex and report values such as sex-specific hazard ratios, mortality ratios, etc.

Methods

- Were there additional inclusion or exclusion criteria beyond the listed search terms?
- A more detailed summary of the number of studies screened, reviewed, and included—along with who performed the screening—would strengthen the methodology. Including a PRISMA diagram would add clarity and rigor.

Results

- Your explanation of atherosclerosis and the role of LDL is clear and helpful.
- The overview of sex-based differences in lipid levels is well-written and effectively communicates the importance of lifetime exposure. Consider including some of this context in the introduction to strengthen the rationale for the review.

- Much of the evidence on sex-based lipid differences is well-established and somewhat dated, making it unclear what new insights this review contributes. If there are recent or emerging findings, highlighting them would reinforce the novelty.
- You may wish to reduce the emphasis on re-establishing sex differences and instead focus more on summarizing new or under-discussed data.
- When introducing the “cholesterol-years” model, please describe how it is calculated (e.g., serial LDL measurements, aggregated lab values) and discuss the feasibility of implementing such modeling in clinical practice.
- The Copenhagen example relies on single-point LDL measurements, which seems to contradict the review’s argument for cumulative LDL modeling. Using an example that incorporates cumulative LDL metrics may better support your thesis.
- The review describes why cumulative burden makes theoretical sense (atherosclerosis is cumulative), but does not provide enough empirical studies demonstrating that cumulative LDL predicts outcomes better than conventional methods.
- You may consider adding more studies that directly model cumulative lipid exposure, use repeat lipid measurements in the same person over decades, or compare cumulative vs. single LDL measurements
- In most reviews, Table 1 summarizes the included studies. Consider adding such a table to synthesize your sources.
- I would consider a break down of studies by cumulative LDL vs. point-measurement since this is a main aim of your study
- The table summarizing lipid-lowering agents should appear after the corresponding discussion to improve flow.
- The section on SERMs and TSECs is compelling—are there additional novel therapeutic strategies or sex-specific approaches worth including?
- You may consider some subheadings within the results section to assist with the flow
- The sex-differences including estrogen’s effects are explained several times across multiple sections, I would suggest consolidating this and focusing more on the concept of life-long exposure and novel treatment approaches

Conclusion

- Please elaborate on the clinical implications. Should clinicians be assessing lifetime lipid exposure rather than relying solely on point measurements? If so, what practical methods exist?
- Are there studies that demonstrate how cumulative LDL assessment improves risk stratification or outcomes? Including these would strengthen the translational relevance of your conclusions.

Unfavourable Curves: Sex-Specific Lipid Metabolism and Lifelong Cardiovascular Risk

Abstract

Background: Dysregulated lipid metabolism, particularly elevated low-density lipoprotein cholesterol (LDL-C), is a major driver of cardiovascular disease (CVD). Sex differences in lipid biology and cumulative LDL-C influence disease onset and severity, yet clinical practice often relies on single time-point measurements.

Methods: This review synthesizes evidence from 84 studies exploring lipid metabolism, sex-specific risk, cumulative LDL-C exposure, and the efficacy of interventional therapies. Key studies of familial hypercholesterolemia (FH), longitudinal LDL-C trajectories, and major clinical trials of statins, ezetimibe, PCSK9 inhibitors, hormone replacement therapy (HRT), and lipoprotein apheresis were examined.

Results: Lifelong elevated LDL-C significantly increases CVD risk; Mendelian-randomization analyses indicate that early reductions confer a 3-fold greater benefit per unit LDL-C than interventions started later in life. Statins effectively lower LDL-C and reduce surrogate markers of atherosclerosis; combination therapy with ezetimibe or PCSK9 inhibitors provides additive benefits. HRT improves lipid profiles but carries cardiovascular and oncologic risks, limiting routine use. Lipoprotein apheresis offers substantial LDL-C and Lp(a) reduction in severe FH. Integration of cumulative lipid data into electronic health records and risk prediction models improves discrimination beyond traditional cross-sectional tools, with benefits for women whose risk trajectories are poorly represented by conventional methods.

Conclusions: Lifetime LDL-C exposure is a critical determinant of CVD risk. Early, sustained intervention tailored to sex and individual risk optimizes prevention. Translating cumulative lipid metrics into clinical practice offers a scalable approach to enhance risk stratification across the lifespan. Future research should address sex-specific responses to therapy and integration of cumulative lipid metrics into clinical practice.

1. Introduction

The cardiovascular system sustains human life by maintaining the continuous circulation of oxygenated blood, nutrients, and metabolic substrates essential to systemic homeostasis; as a result, its failure—even transiently—carries severe physiological consequences (Chaudhry et al., 2022). Cardiovascular disease (CVD) encompasses a spectrum of disorders affecting the heart and its vasculature, most prominently coronary artery disease, cerebrovascular disease, and heart failure, and remains the leading global cause of death, accounting for approximately 17.9 million deaths annually or nearly one-third of all global mortality (Lopez et al., 2023; World Health Organization, 2019; Benjamin et al., 2018). It also constitutes an immense economic burden, generating an estimated $237 billion in indirect annual costs and is projected to exceed $368 billion by 2035 (Dunbar et al., 2018). Although the past half-century has seen remarkable advances in diagnostic imaging, pharmacological therapy, and surgical intervention that have improved acute outcomes, the overall prevalence of CVD continues to climb due to factors such as population aging, lifestyle-related risk factors, and widening health disparities (Zhou et al., 2022). The persistence of this burden thus highlights the need to interrogate the

biological determinants that shape cardiovascular risk longitudinally across the lifespan, rather than at isolated moments in time.

Among these determinants, dysregulation of lipid metabolism has long been recognized as central to the pathogenesis of atherosclerotic disease (Steinbeck et al., 2025). Atherosclerosis—characterized by the accumulation of lipid-rich plaques within the arterial wall—develops gradually over decades and underlies most ischemic cardiovascular events (Pahwa & Jialal, 2023). While the cellular and molecular mechanisms governing plaque initiation and progression are well-established, with endothelial dysfunction, oxidative modification of low-density lipoprotein cholesterol (LDL-C) and chronic vascular inflammation primary among them, these processes are inherently time-dependent and modulated by systemic metabolic and hormonal states (Popa-Fotea et al., 2023). Consequently, lipid metabolism serves as both a mechanistic and epidemiological bridge between molecular pathophysiology and population-level CVD risk.

The risk of CVD demonstrates marked demographic heterogeneity. Men generally exhibit a higher incidence at younger ages, whereas the risk for women increases sharply following the onset of menopause, narrowing the sex gap in later decades (Merz & Cheng, 2016). The mechanistic basis of this disparity remains incompletely understood, though converging evidence implicates differences in lipid metabolism as a major driver (Robinson et al., 2022). Estrogen-mediated lipid regulation, characterized by enhanced hepatic LDL clearance and increased high-density lipoprotein cholesterol (HDL-C), is thought to contribute to the relative cardioprotection observed in premenopausal women (Palmisano et al., 2017). The postmenopausal decline in estrogen attenuates these effects, leading to adverse lipid shifts and accelerated atherosclerotic risk (Raj et al., 2023). By contrast, men, lacking this hormonal modulation, exhibit elevated LDL-C and reduced HDL-C levels throughout life, consistent with their earlier disease onset (Pérez-López et al., 2010). Although these sex differences are well-documented, their interaction with *lifelong* lipid exposure remains insufficiently characterized.

Cardiovascular risk is shaped not only by absolute lipid concentrations at a single point in time, but by cumulative exposure to atherogenic lipoproteins across the lifespan. Sex-specific lipid trajectories, particularly those shaped by hormonal transitions, may therefore exert disproportionate influence on lifetime cardiovascular risk that is not captured by conventional point-based risk estimates. Indeed, current clinical risk assessment frameworks rely predominantly on single time-point lipid measurements, which may inadequately capture the cumulative nature of atherogenic exposure. Such approaches can underestimate early-life risk, misclassify individuals with historically elevated cholesterol but later treatment, and obscure sex-specific trajectories shaped by hormonal transitions (Zhang et al., 2021; Seidemann et al., 2024). Emerging evidence from Mendelian randomization studies and longitudinal cohorts suggests that the *duration* and *timing* of LDL-C exposure, rather than isolated values, are critical determinants of cardiovascular outcomes, with early reductions conferring disproportionately greater benefit than later intervention.

In this context, cumulative lipid burden may be conceptualized as the time-integrated exposure to circulating atherogenic lipoproteins, operationalized through metrics such as “cholesterol-years” or LDL years, serial aggregation of repeated lipid measurements, or genetic proxies for lifelong LDL-C elevation. However, the clinical implementation of such frameworks remains limited, and sex-specific validation is notably sparse.

Accordingly, this literature review synthesizes current evidence to evaluate cumulative lipid exposure as a determinant of cardiovascular risk across the lifespan, with particular attention to sex-specific biology. Rather than re-establishing known sex differences in lipid profiles, this review critically examines how cumulative LDL-C burden has been measured, where empirical support exists, and where significant gaps, especially

regarding sex-stratified risk estimation, persist. By integrating mechanistic insights with epidemiological data, this review aims to clarify the translational potential of cumulative lipid metrics and to identify key methodological and evidentiary barriers that must be addressed to advance sex-specific cardiovascular prevention strategies.

2. Methods

Literature search strategy

A structured literature search was conducted to identify peer-reviewed studies examining the relationship between lipid metabolism, cholesterol regulation, sex-specific biological differences, and CVD risk. The primary database used was PubMed, with supplementary searches performed in Scopus and Google Scholar to ensure comprehensive coverage of both biomedical and biochemical research. The search encompassed publications available in English up to October 2025.

Search terms included, but were not limited to, combinations of the following keywords and Boolean operators: “cardiovascular disease” OR “atherosclerosis” AND “cholesterol” OR “lipids” OR “lipid metabolism” AND “sex differences” OR “gender differences” OR “menopause” OR “estrogen”. Additional terms such as “hormonal regulation”, “LDL-C”, “HDL-C”, “reverse cholesterol transport”, and “cumulative lipid burden” were incorporated in secondary searches to refine topic specificity. Reference lists of major reviews and landmark cohort studies were also manually screened to capture relevant primary research not indexed under these search terms.

Inclusion and exclusion criteria

Studies were selected based on predefined inclusion and exclusion criteria. Eligible studies met one or more of the following criteria: large-scale epidemiological or longitudinal cohort studies examining serum lipid levels, aging, and cardiovascular outcomes in human populations; genetic or Mendelian randomization studies evaluating lifelong exposure and cardiovascular risk; mechanistic or biochemical studies elucidating pathways by which sex hormones influence lipid metabolism and atherogenesis; and review articles synthesizing lipid metabolism and CVD risk, included to contextualize primary findings.

Studies were excluded if they were non-peer-reviewed sources, case reports, editorials, or conference abstracts; focused exclusively on animal or in vitro models without clear translational relevance to human lipid metabolism; or addressed metabolic disorders unrelated to cardiovascular lipid metabolism.

Screening and data extraction

The literature search yielded approximately 1,200 records across all databases. After removal of duplicates (~200), ~1000 records underwent title and abstract screening. Of these, ~850 articles were excluded based on relevance, leaving ~150 full-text articles assessed for eligibility. Following full-text review, 84 articles met inclusion criteria and were incorporated into the final qualitative synthesis.

Screening, eligibility assessment, and data extraction were performed by the author. Extracted data included study design, population characteristics, lipid metrics assessed (e.g., point-based LDL-C versus cumulative measures), duration of follow-up, sex-stratified analyses, and reported cardiovascular outcomes.

A PRISMA flow diagram summarizing the study selection process is provided in Figure 1.

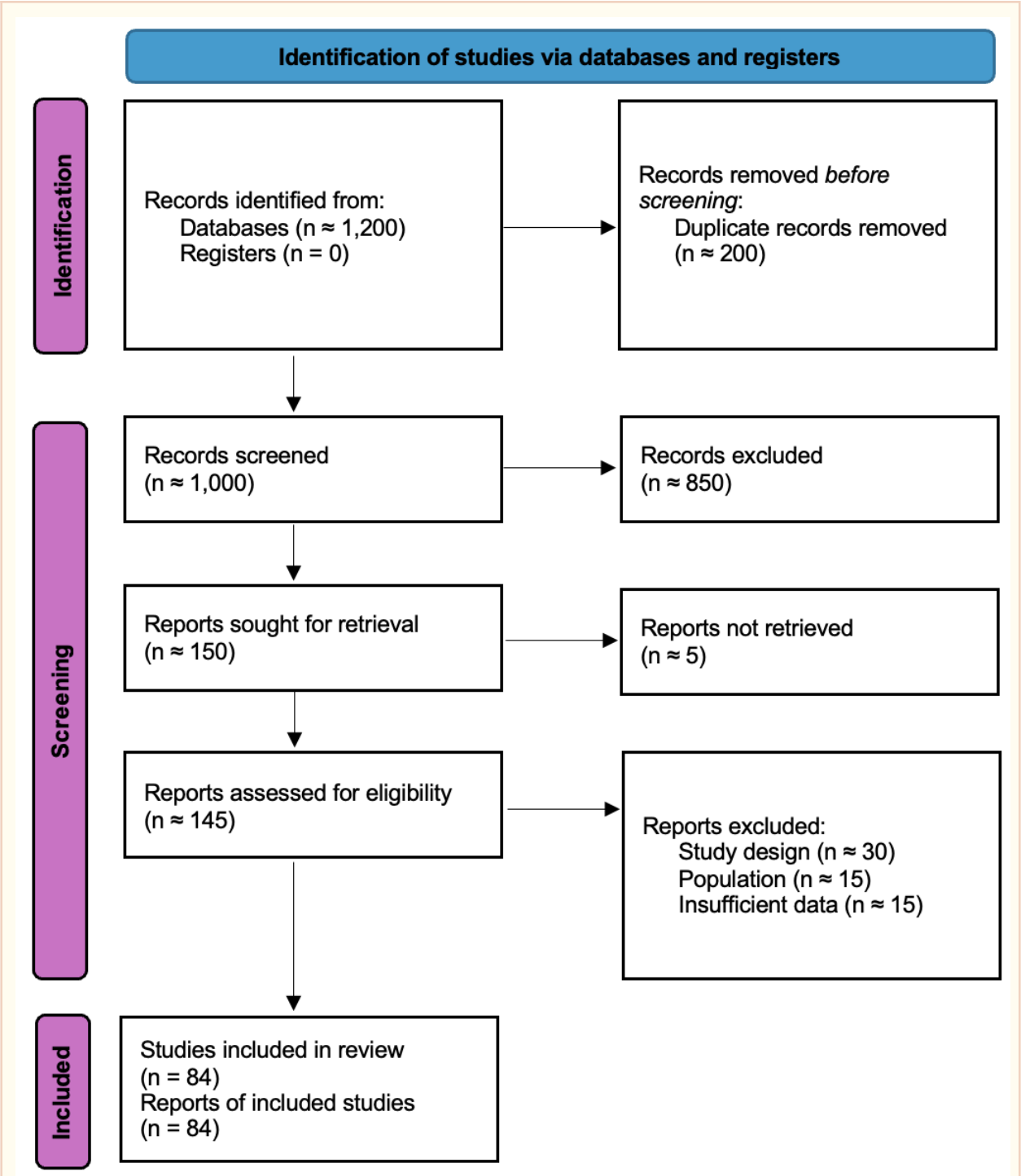

Figure 1. PRISMA flow diagram summarizing the literature search and study selection process. The

literature search yielded approximately 1,200 records across databases, with ~200 duplicates removed. Title and abstract screening excluded ~850 articles, and 150 full-text articles were assessed for eligibility. Following full-text review, 84 studies were included in the final qualitative synthesis.

Synthesis strategy

Included studies were grouped thematically according to whether they employed traditional point-based lipid measurements or cumulative lipid exposure metrics. Within these groups, evidence was further synthesized based on sex-specific analyses, age-related lipid trajectories, and cardiovascular outcomes. This approach enabled a direct comparison between conventional risk paradigms and emerging cumulative exposure frameworks.

3. Results

Collectively, lipid biology is both a causal and modulatory factor in cardiovascular disease. Understanding how lipids circulate, modify, and accumulate within arterial walls is essential to contextualize both epidemiological trends and sex-based disparities in disease burden. Beyond the absolute concentrations of circulating lipoproteins, the cumulative exposure to atherogenic lipids over the lifespan is a central determinant of disease trajectory. This passage provides the biochemical context for understanding sex- and age-related heterogeneity in cardiovascular risk, which will be explored in greater depth in subsequent sections.

Lipid-driven atherosclerosis as a cumulative process

Lipid metabolism is central to the etiology of CVD, primarily through its influence on atherosclerotic plaque formation and progression. Atherosclerosis, the predominant pathological substrate underlying most ischemic cardiovascular events, is a progressive process initiated by endothelial dysfunction, in which the vascular endothelium loses its ability to regulate vascular tone and maintain barrier integrity (Park & Park, 2015). This impairment facilitates the subendothelial retention of apolipoprotein B-containing lipoproteins, primarily low-density lipoprotein cholesterol (LDL-C), which represents the principal atherogenic lipoprotein species (Tabas et al., 2007).

Upon infiltration into the arterial intima, LDL particles undergo oxidative and enzymatic modifications, producing oxidized LDL (oxLDL) (Jiang et al., 2022). OxLDL has multiple atherogenic properties, including upregulation of endothelial cell adhesion molecules, recruitment of circulating monocytes, and induction of pro-inflammatory signaling cascades (Poznyak et al., 2021). Monocytes differentiate into macrophages within the intima, engulfing oxLDL via scavenger receptors, and as lipid accumulation exceeds cellular processing capacity, macrophages transform into foam cells and form the fatty streak—the earliest visible lesion of atherosclerosis (Chistiakov et al., 2016; Ouyang et al., 2023).

Over time, smooth muscle cells migrate into the intima and deposit extracellular matrix, creating a fibrous cap over a lipid-rich necrotic core (Harman & Jørgensen, 2019). This plaque can remain stable for years, but oxidative stress and inflammatory activity promote thinning of the fibrous cap, increasing the likelihood of rupture, which subsequently exposes thrombogenic contents to circulating blood and precipitates acute coronary syndromes such as MI (Loftus, 2011). This process is thus inherently time dependent. More specifically, LDL particles that circulate for longer periods are more likely to undergo oxidative modification and arterial

retention, increasing plaque burden incrementally over decades (Akyol et al., 2025). Consequently, atherosclerosis is fundamentally cumulative, with lifetime exposure to atherogenic lipoproteins representing a key determinant of disease severity (Almohtasib et al., 2024). Atherosclerosis thus reflects both the magnitude and duration of LDL-C exposure, supporting a cumulative exposure or a “cholesterol-years” model of development. This framework provides the mechanistic foundation for interpreting sex- and age-related heterogeneity in cardiovascular risk.

Figure 2 provides a schematic overview of the molecular pathways governing lipid metabolism.

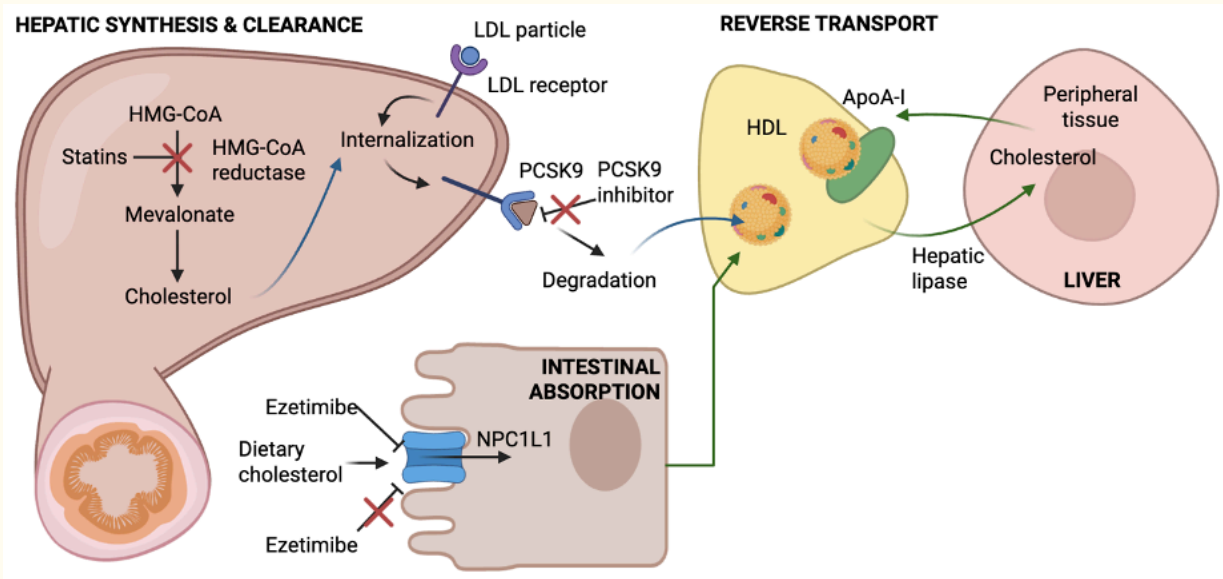

Figure 2. Molecular mechanisms of lipid metabolism and therapeutic intervention points. Simplified schematic illustrating hepatic cholesterol synthesis, intestinal absorption, LDL receptor-mediated clearance, and reverse cholesterol transport, highlighting targets of statins, ezetimibe, PCSK9 inhibitors, and hormone-mediated regulation. Created in BioRender.

The interactions between lipid species further modulate atherosclerotic risk. While LDL-C contributes directly to plaque formation, high-density lipoprotein cholesterol (HDL-C) mediates protective mechanisms through reverse cholesterol transport, whereby excess cholesterol is effluxed from peripheral tissues and transported to the liver for excretion (Ouimet et al., 2019).

Sex-specific lipid trajectories across the lifespan

Epidemiological data consistently demonstrate pronounced sex-based differences in both lipid metabolism and cardiovascular risk trajectories. Men generally exhibit higher LDL-C and triglyceride concentrations, coupled with lower HDL-C levels, beginning as early as adolescence (Russo et al., 2015). These differences correlate with earlier onset and greater lifetime incidence of atherosclerotic CVD (Rodgers et al., 2019). In contrast, premenopausal women typically maintain a more favourable lipid profile, characterized by lower LDL-C and elevated HDL-C levels, which correspond to their reduced risk of coronary events prior to menopause (Ryczkowska et al., 2022).

Figure 3 illustrates longitudinal lipid trajectories for men and women across adulthood.

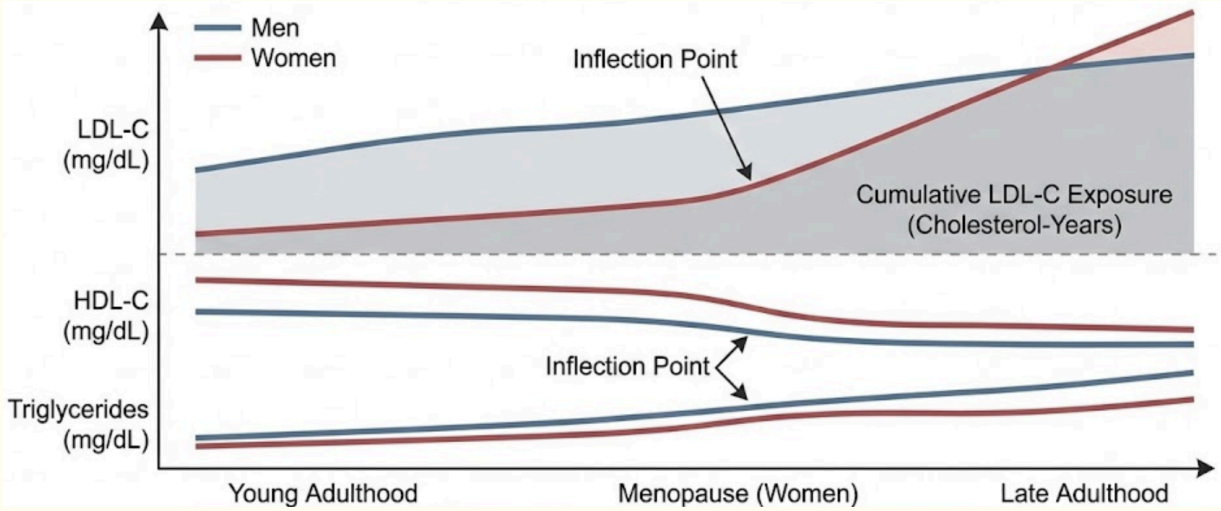

Figure 3. Sex-specific lipid trajectories and cumulative cardiovascular risk. Longitudinal trajectories of LDL-C, HDL-C, and triglycerides in men and women across adulthood. Inflection points highlight the midlife rise in LDL-C among women during the menopausal transition. Shaded areas indicate cumulative LDL exposure ("cholesterol-years"), illustrating differences in lifetime atherogenic burden and periods of elevated cardiovascular risk. Created in BioRender.

This divergence is largely attributed to the hormonal regulation of hepatic lipid processing. Androgen-dominant metabolic environments in males promote increased hepatic lipase activity, accelerating HDL catabolism and reducing HDL-C concentration (Herbst et al., 2003). Concurrently, reduced LDL receptor density in hepatocytes contributes to slower LDL clearance from the circulation; these features collectively produce an early-life metabolic phenotype conducive to lipid retention and vascular injury (Pirahanchi et al., 2023).

Sex hormones exert a considerable regulatory effect on lipid metabolism, contributing to observed demographic patterns in CVD incidence (Robinson et al., 2022). The onset of menopause represents a pivotal inflection point in female lipid physiology. Estrogen—the principal modulator of lipid homeostasis in women—exerts multifaceted effects on lipoprotein mechanisms, upregulating hepatic LDL receptor expression, facilitating LDL particle uptake and degradation, and promoting apolipoprotein A-I (ApoA-I) synthesis, the major protein constituent of HDL (Nii et al., 2016; Palmisano et al., 2018). These combined mechanisms confer a premenopausal cardioprotective lipid profile in women (Ryczkowska et al., 2022). Following menopause, declining estrogen levels attenuate these protective mechanisms; LDL-C increases, HDL-C decreases, and women's cardiovascular risk rises sharply (Ryczkowska et al., 2022). By contrast, men lack this hormonal protection throughout life, which may explain their earlier onset of CVD (Rodgers et al., 2019). Moreover, estrogen stimulates the activity of ATP-binding cassette transporters (ABCA1 and ABCG1) involved in cholesterol efflux, thereby augmenting reverse cholesterol transport (Bao et al., 2023). These hormonal transitions shift women from a low cumulative LDL exposure trajectory toward a rapidly accelerating risk profile in midlife, narrowing the sex gap in atherosclerotic cardiovascular disease (ASCVD incidence.

Beyond circulating estrogen, sex-specific lipid metabolism is modulated by androgens and progesterone. Androgens, which predominate in males, exert multiple pro-atherogenic effects, primarily through hepatic lipid regulation (Xu et al., 2022). Elevated androgens increase hepatic lipase activity, accelerating the catabolism of HDL particles and leading to smaller, less functional HDL that is less effective in reverse cholesterol transport (Kantor et al., 1985). Additionally, androgen exposure favors the production of small, dense LDL particles, which are more susceptible to oxidation, exhibit increased arterial retention, and undergo atherogenic modification

(Vekic et al., 2022). These molecular and structural alterations provide a mechanistic basis for the higher prevalence of early-onset cardiovascular disease observed in males.

In contrast, progesterone, a dominant female sex hormone during the luteal phase and pregnancy, influences lipid metabolism in a more nuanced manner. Progesterone modulates HDL functionality by altering particle composition and may affect the distribution of LDL subfractions, though the net cardiovascular impact remains less clearly defined (Corsini et al., 1988). Importantly, these effects are context-dependent, influenced by hormonal milieu, age, and concomitant estrogen exposure. Estrogen receptor signaling, mediated by ERα and ERβ, plays a pivotal role in hepatocyte lipid handling, regulating transcription of key genes including LDL receptor, apolipoprotein A-I, and enzymes involved in cholesterol esterification and bile acid synthesis (Zhu et al., 2018). Additionally, estrogen modulates sterol regulatory element-binding protein (SREBP) pathways, which are central to endogenous cholesterol synthesis and intracellular lipid homeostasis (Sakai & Rawson, 2001). Collectively, these hormonal and intracellular mechanisms underlie the observed divergence in lipid profiles between males and females across the lifespan, contributing to delayed atherosclerotic development in premenopausal women and accelerated risk in men and postmenopausal women.

The effects of sex hormones extend beyond circulating lipoproteins to cellular processes in the vascular wall. Estrogen enhances endothelial nitric oxide synthase (eNOS) activity, promoting vasodilation and reducing oxidative stress, while androgens may favor pro-inflammatory cytokine expression and endothelial dysfunction (MacRitchie et al., 1997). These vascular effects amplify the consequences of sex-specific lipid profiles, reinforcing the higher baseline risk of atherogenesis in males and the protective effect of premenopausal estrogen in females.

In addition to conventional lipid fractions, lipoprotein(a) (Lp(a)) represents a genetically determined, highly atherogenic lipoprotein whose plasma concentration is largely stable throughout life and minimally influenced by diet, exercise, or conventional lipid-lowering therapies (Farzam et al., 2024). Structurally, Lp(a) consists of an LDL-like particle covalently bound to apolipoprotein(a), a glycoprotein homologous to plasminogen, which confers prothrombotic properties in addition to its atherogenic potential (Farzam et al., 2024). Elevated Lp(a) levels have been associated with accelerated coronary artery disease, calcific aortic valve disease, and heightened inflammatory signaling in the vascular endothelium (Wambua et al., 2025).

The clinical impact of Lp(a) appears to differ by sex and hormonal status. In premenopausal women, Lp(a)-related risk is partially mitigated by estrogen-mediated enhancement of LDL receptor expression and lipoprotein clearance (Corral et al., 2024). Postmenopausal women, however, experience a disproportionate increase in atherosclerotic cardiovascular disease (ASCVD) risk when Lp(a) levels are elevated, potentially due to the combined effects of increased LDL-C, loss of estrogen-driven hepatic clearance, and heightened inflammatory susceptibility in the vascular wall (Roeters van Lennep et al., 2023).

Consequently, these well-established sex differences have been reframed as divergent cumulative exposure trajectories shaped by hormonally timed inflection points rather than as static biological distinctions. Recent longitudinal analyses emphasize that cardiovascular risk divergence arises from differences in *when* and *for how long* individuals are exposed to atherogenic lipid environments, rather than from fixed sex-based lipid set points (Wilkins et al., 2024; Zheutlin et al., 2025). This temporal reframing has shifted the field away from cross-sectional lipid comparisons toward life-course modeling approaches that better capture the delayed but accelerated risk observed in postmenopausal women. Such findings highlight the need to integrate sex, age, and duration of exposure into cardiovascular risk assessment rather than treating sex differences as isolated phenomena.

Longitudinal evidence of cumulative lipid burden

As endogenous estrogen production declines during the menopausal transition, these regulatory mechanisms wane, leading to measurable alterations in serum lipid composition (Patel et al., 2025). The extent and timing of these changes have been captured through large-scale prospective cohorts, including the Framingham Offspring Study (FOS) and the Study of Women's Health Across the Nation (SWAN) (Duncan et al., 2019; El Khoudary et al., 2019). More specifically, these cohorts provide empirical support for cumulative lipid exposure as a superior predictor of cardiovascular outcomes compared with single-point LDL measurements.

FOS, a longitudinal cohort initiated in 1971 to follow the descendants of the original Framingham Heart Study participants, provides some of the most comprehensive sex-stratified analyses of lipid trajectories and cardiovascular outcomes. Among 3,875 participants (54% women; mean age 48 years) followed between 1979 and 2014, investigators identified five distinct trajectories of total cholesterol (TC), LDL-C, and HDL-C across adulthood (Duncan et al., 2019). Importantly, women exhibited marked inflection points in LDL-C and HDL-C levels during midlife, consistent with the perimenopausal transition, where average LDL-C concentrations increased by approximately 10–15%, while HDL-C declined modestly—changes that paralleled reductions in circulating estradiol rather than chronological aging or body mass index (Ryczkowska et al., 2022). This finding reinforces that timing and duration of exposure, rather than absolute midlife LDL-C alone, drive long-term risk.

Elevated lipid trajectories were strongly associated with future ASCVD and mortality. Participants maintaining LDL-C >155 mg/dL, TC >240 mg/dL, or non-HDL-C >180 mg/dL had over a twofold increase in ASCVD and all-cause mortality risk compared with those maintaining optimal lipid levels (HR_{ASCVD} = 5.09 [95% CI: 1.54–16.85]; HR_{death} = 4.04 [1.84–8.89]) (Duncan et al., 2019). Conversely, persistently low HDL-C (<40 mg/dL) was associated with a nearly 4-fold higher ASCVD risk compared with concentrations >70 mg/dL (Duncan et al., 2019). These findings reinforce the concept of cholesterol-years—that is, cumulative exposure to atherogenic lipoproteins—as a more precise determinant of lifetime cardiovascular risk than any single lipid measurement (Wilkins et al., 2024). From a mechanistic perspective, these observations align with the decline in hepatic LDL receptor expression post-menopause, leading to reduced LDL clearance and prolonged lipoprotein residence time within circulation, thereby increasing the probability of oxidative modification and endothelial retention (P, 2025). FOS thus provides population-scale confirmation of the biochemical mechanisms previously discussed.

Complementing the Framingham data, SWAN—a multi-ethnic, prospective cohort initiated in 1994—has characterized the dynamic lipid changes across the menopausal transition in greater temporal resolution and demonstrated that the steepest increases in LDL-C occurred within a narrow window surrounding the final menstrual period, temporally aligned with estradiol decline. SWAN followed over 3,000 premenopausal women aged 42-52 from diverse ethnic backgrounds (Caucasian, African-American, Chinese, Japanese, and Hispanic) for over two decades, incorporating both hormonal and metabolic assessments at annual intervals (El Khoudary et al., 2019; Derby et al., 2009). Longitudinal analyses across the menopausal stages revealed that the steepest rise in LDL-C and total cholesterol levels occurred within a two-year window surrounding the final menstrual period (FMP), temporally coinciding with the estradiol nadir (El Khoudary et al., 2021). These changes were most pronounced during early postmenopause, when estrogen depletion accelerates hepatic lipid remodeling (El Khoudary et al., 2021).

Mechanistically, SWAN's metabolic substudy highlighted that declining estrogen levels were associated with increased hepatic lipase activity and reduced ApoA-I concentrations, attenuating HDL particle maturation and impairing reverse cholesterol transport (Woodard et al., 2011). Additionally, small dense LDL particles became

increasingly prevalent in the years following menopause, a pattern associated with heightened atherogenic potential due to their greater arterial wall penetrance and oxidative susceptibility (He et al., 2025). Importantly, SWAN's findings highlight menopause as a biologically discrete period of accelerated lipid remodeling that materially contributes to cumulative atherogenic burden.

Taken together, the Framingham and SWAN cohorts provide converging evidence that the menopausal transition represents a biologically distinct period of lipid remodeling with direct implications for cardiovascular risk. Framingham emphasizes the cumulative, long-term impacts of rising LDL-C post-menopause on clinical outcomes, while SWAN delineates the temporal and mechanistic sequence of lipid alterations accompanying hormonal declines; its inclusion of diverse populations underscores that, while hormonal decline is universal, its phenotypic lipid effects are modulated by race, diet, and genetic background.

When contextualized within the broader framework of lipid biology, these findings reinforce the notion that lifetime exposure to atherogenic lipoproteins—modulated by the hormonal milieu—is a principal determinant of CVD onset and severity. This cumulative exposure framework integrates both male and female trajectories: men experience a steady accrual of risk beginning early in adulthood due to persistently higher LDL-C levels, whereas women's risk accelerates sharply post-menopause as estrogen-mediated lipid regulation deteriorates. Such evidence provides a mechanistic and epidemiological rationale for sex-specific therapeutic approaches, discussed in subsequent sections, emphasizing the potential for early lipid intervention in premenopausal women to mitigate post-menopausal risk acceleration.

Empirical support for the cholesterol-years model

The primary aim of this review is to evaluate empirical evidence supporting cumulative lipid exposure models and to examine whether these approaches reveal sex-specific associations with cardiovascular outcomes beyond conventional point-based measurements. While relatively few studies explicitly operationalize cumulative cholesterol metrics, a growing body of longitudinal, genetic, and cohort-based evidence demonstrates that duration- and burden-based lipid exposure more accurately predicts cardiovascular risk, particularly when sex- and life-stage–specific trajectories are considered.

Indeed, while acute lipid measurements are standard clinical practice, growing evidence emphasizes that cumulative exposure to atherogenic lipoproteins, rather than isolated LDL-C levels, is the principal determinant of CVD risk (Zheutlin et al., 2025). Prolonged circulation of LDL particles increases the probability of their oxidative modification and subsequent arterial retention, accelerating atherogenesis (Maiolino et al., 2013). Indeed, accumulating epidemiological and genetic evidence supports a *cholesterol-years* model of atherogenesis in which the duration of exposure to atherogenic lipoproteins materially influences lifetime risk of coronary heart disease (CHD) (Zheutlin et al., 2025). In other words, genetic and modeling studies provide direct evidence that cumulative LDL exposure predicts cardiovascular outcomes more accurately than conventional point-based metrics.

Operationally, cumulative LDL exposure ("cholesterol-years") is calculated by aggregating serial LDL-C measurements over time, typically as the area under the LDL-C-time curve or as a time-weighted average of repeated values across adulthood (Ference et al., 2012). In genetic studies, this exposure is approximated through lifelong LDL-C differences conferred by specific variants, providing a proxy for sustained exposure independent of treatment or behaviour (Ference et al., 2012). In observational cohorts, cumulative burden has been modeled using repeated laboratory measurements collected at regular intervals, enabling estimation of total LDL exposure across decades (Zhang et al., 2021).

Mendelian-randomization meta-analyses by Ference et al. provide strong support for the cholesterol-years paradigm. Ference et al. integrated nonoverlapping data from 312,321 participants across nine polymorphisms affecting LDL-C regulation. Each mmol/L genetically lower LDL-C was associated with a 54.5% reduction in CHD risk (95% CI: 48.8–59.5%), reflecting a ~3-fold greater risk reduction per unit LDL-C than statin therapy initiated later in life ($p = 8.43 \times 10^{-19}$) (Ference et al., 2012). These results demonstrate that early and sustained reductions in LDL-C produce disproportionately larger cardiovascular benefits, supporting the notion that cumulative LDL exposure, rather than cross-sectional levels alone, governs atherosclerotic progression. Conceptually, these observations have been framed as the cholesterol-years or lifelong exposure model: the findings strongly support an area-under-the-curve model of LDL exposure across the lifespan that appears to predict disease more accurately than a single midlife measurement (Ference et al., 2012).

Complementing genetic findings, population-level analyses further corroborate this framework. Zhang et al. 2021 pooled data from four prospective cohorts (18,288 participants; 56.4% women; mean age 56.4 ± 3.7 years; median follow-up ≈ 16 years) (Zhang et al., 2021). Using cumulative LDL-C, time-weighted average (TWA), and LDL-C slope metrics, the study found that both cumulative LDL-C and TWA LDL-C were independently associated with incident CHD even after adjustment for the most recent midlife LDL-C and traditional CVD risk factors (Zhang et al., 2021). By contrast, the LDL-C slope alone was not significantly associated with CHD after accounting for midlife levels, reinforcing that the area *under the LDL curve* (cumulative burden) rather than transient changes in LDL-C is the critical metric (Zhang et al., 2021). Thus a lifelong lipid exposure model is translationally relevant once mechanistic insights from genetic studies are extended into population-level observations.

Navar-Boggan et al. provide some of the strongest longitudinal evidence that cumulative lipid exposure predicts cardiovascular outcomes more accurately than single time-point lipid measurements. Using data from the Framingham Offspring Cohort, the authors examined 1,478 adults free of cardiovascular disease through age 55 and quantified duration of moderate hyperlipidemia in early adulthood (defined as non-HDL cholesterol ≥160 mg/dL). Over a median 15-year follow-up, CHD incidence increased in a clear dose-dependent manner with longer cumulative exposure: 4.4% among individuals with no exposure, 8.1% among those with 1-10 years of exposure, and 16.5% among those with 11-20 years of exposure ($P < 0.001$) (Navar-Boggan et al., 2015). Importantly, this association persisted after adjustment for contemporaneous lipid levels at age 55 and other cardiovascular risk factors, with a 39% increase in CHD risk per decade of hyperlipidemia exposure (HR 1.39; 95% CI 1.05-1.85) (Navar-Boggan et al., 2015). Notably, 85% of participants with prolonged hyperlipidemia would not have met statin treatment thresholds under contemporary 10-year risk-based guidelines, highlighting systematic underestimation of early-life risk (Navar-Boggan et al., 2015). Even among individuals not considered statin candidates at age 55, cumulative exposure remained independently associated with future CHD (adjusted HR 1.67; 95% CI 1.06-2.64) (Navar-Boggan et al., 2015). These findings demonstrate that cumulative lipid burden captures clinically meaningful risk missed by point-in-time lipid measurements and provide direct empirical support for lifetime exposure models of atherosclerotic risk. Although Navar-Boggan et al. did not stratify outcomes by sex, the findings are particularly salient when interpreted alongside sex-specific lipid trajectories observed in Framingham and SWAN, where women experience delayed but accelerated LDL accumulation post-menopause. Together, these studies suggest that cumulative lipid exposure may systematically underestimate risk in women when assessed using midlife point measurements alone.

Further evidence comes from the Copenhagen General Population Study (CGPS) which enrolled 91,131 individuals between 2003 and 2015, with a mean follow-up of 7.7 years (Mortensen & Nordestgaard, 2020). During this period, 1,515 first myocardial infarctions (MI) and 3,389 atherosclerotic cardiovascular events occurred, where each 1.0 mmol/L increase in LDL-C was associated with a 34% higher risk of MI (HR: 1.34; 95%

CI: 1.27–1.41) and a 16% higher risk of ASCVD overall (HR: 1.16; 95% CI: 1.12–1.21) (Mortensen & Nordestgaard, 2020). Notably, risk was amplified in older adults (aged 70–100 years) and in individuals with very high LDL-C (≥5.0 mmol/L), consistent with the notion that both absolute levels and cumulative exposure exacerbate atherosclerotic outcomes (Mortensen & Nordestgaard, 2020). Notably, the CGPS relies on single-point LDL-C measurements, which limits its ability to directly assess cumulative lipid exposure. However, its findings nevertheless align with cumulative risk models by demonstrating amplified risk at older ages, when lifetime LDL burden is greatest, but highlight the need for studies incorporating repeated measurements to more accurately quantify exposure over time.

Complementing these observational studies, population screening for heterozygous familial hypercholesterolemia (FH) demonstrates the extreme consequences of lifelong elevated LDL-C. FH, an autosomal dominant genetic disorder caused by mutations in genes critical for LDL clearance that impair hepatic LDL uptake, is characterized by markedly elevated plasma LDL-C concentrations from birth (Warden et al., 2024). Prevalence estimates range from 1/500 to 1/200 in Northern European populations, yet <1% of affected individuals are diagnosed in most countries (Nordestgaard et al., 2013). Individuals with untreated FH experience up to a 13-fold increased risk of CHD, suggesting that prolonged and substantial elevations in LDL-C from early life dramatically accelerate atherosclerosis (Nordestgaard et al., 2013). FH thus provides an application of the cholesterol-years paradigm: both the magnitude and duration of LDL-C elevation are critical determinants of cardiovascular risk, and the findings reinforce the mechanistic link between lifelong LDL burden and atherosclerotic disease.

Collectively, converging evidence from genetic, longitudinal, and clinical studies emphasizes that cardiovascular risk is not merely a function of LDL-C concentration at a single point in time, but rather of its cumulative exposure across the lifespan. Thus, early and sustained lipid control, rather than reactive prevention in midlife, yields disproportionately greater protection against lifetime cardiovascular risk. Table 1 synthesizes key studies comparing hookup between cumulative LDL metrics and traditional point-based measurements, illustrating the relative paucity but growing importance of longitudinal exposure modeling in cardiovascular risk assessment.

Study	Population	LDL Metric	Comparator	Outcome	Key Finding	Clinical Implication
Ference et al., 2012	Mendelian randomization meta-analysis, n > 300,000	Genetically mediated lifelong LDL reduction	Statin-era LDL reduction	CHD incidence	Lifelong LDL lowering yields ~3× greater risk reduction per mmol/L	Timing and duration of LDL exposure are critical
Zhang et al., 2021	4 pooled cohorts, n > 18,000; 56% women	Cumulative LDL-C (AUC), time-weighted average	Most recent LDL-C	Incident CHD	Cumulative and TWA LDL independently predicted CHD; LDL slope did not	Area-under-the-curve LDL more informative than point or slope
Navar-Boggan et al., 2015	Framingham Offspring Cohort; n=1,478; free of CVD to age 55	Duration of non-HDL-C ≥160mg/dL ("years of exposure")	Single LDL/non-HDL at age 55	CHD incidence	CHD risk ↑ dose-dependently with longer exposure (HR 1.39 per decade), independent of contemporaneous lipids	Duration of exposure captures risk missed by midlife measurements
CGPS (Mortensen & Nordestgaard,	Copenhagen General	Single LDL-C	—	MI, ASCVD	Higher LDL associated with	Highlights limitations of

2020)	Population Study; n=91,131				higher risk, amplified at older ages	single-point LDL
Nordestgaard et al., 2013; Warden et al., 2024 (FH studies)	Population screening cohorts; heterozygous FH (~1/200–1/500 prevalence)	Lifelong genetically elevated LDL-C from birth	Non-FH population (normal LDL exposure)	CHD, MI	Untreated FH associated with up to 13-fold increased CHD risk due to lifelong LDL elevation	Demonstrates extreme consequences of cumulative LDL exposure; magnitude *and* duration determine risk

Table 1. Key studies comparing cumulative LDL exposure metrics with traditional point-based lipid measurements. Summary of major studies evaluating the relationship between cumulative LDL-C metrics (e.g., cholesterol-years, area under the LDL-C curve, time-weighted averages) and cardiovascular outcomes, with comparison to traditional single-point measurements. The table highlights population characteristics, lipid metrics assessed, comparators, outcomes, key findings, and clinical implications.

From a clinical standpoint, implementation is increasingly feasible as electronic health records now capture longitudinal lipid data across multiple life stages. While early-life measurements remain sparse in many populations, even partial cumulative estimates derived from adolescence or early adulthood onward may nevertheless capture a substantial proportion of lifetime atherogenic exposure (Zheutlin et al., 2025). Such partial cumulative modeling may substantially improve risk stratification as compared with single-point assessments, particularly in populations experiencing hormonally mediated lipid shifts. As longitudinal data availability continues to expand and cumulative exposure metrics become more readily integrated into existing cardiovascular risk calculators, cholesterol-years modeling represents a practical and scalable approach to refining lifetime cardiovascular risk assessment. The clinical performance and predictive value of longitudinal risk factor integration are discussed further in the subsection *Emerging sex-specific strategies for mitigating cumulative lipid burden* below, where emerging modeling approaches demonstrate improved discrimination and reclassification beyond traditional cross-sectional tools.

Therapeutic strategies and sex-specific limitations

Given the centrality of cumulative LDL-C exposure in atherosclerosis, therapeutic interventions aim to reduce circulating LDL-C levels, enhance clearance, or modify lipid metabolism to slow plaque progression.

Statins remain the first-line therapy for both primary and secondary prevention of CVD. Mechanistically, statins inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis in hepatocytes (Bansal & Cassagnol, 2023). Reduced intracellular cholesterol triggers upregulation of LDL receptors on the liver surface, promoting the uptake of circulating LDL particles and lowering plasma LDL-C concentrations (Trapani et al., 2012). In children with heterozygous FH, statins have been shown to substantially reduce LDL-C levels and slow progression of atherosclerosis. A systematic review including nine randomized placebo-controlled trials (1,177 participants; median follow-up 24 weeks) found statin therapy reduced mean LDL-C by 32.15% (95% CI: 29.4–34.9%) and produced measurable improvements in brachial artery flow-mediated dilatation (2.7% higher; 95% CI: 0.42–4.98) and carotid intima-media thickness (CIMT) (mean change 0.01 mm lower) relative to placebo, both surrogate markers of atherosclerotic burden (Vuorio et al., 2019). Adverse events, including myopathy and changes in liver enzymes, were rare and comparable to placebo, supporting the safety of early statin initiation in pediatric populations (Vuorio et al., 2019).

Ezetimibe, an adjunct to statins, inhibits the NPC1L1 transporter in the intestinal brush border, reducing absorption of dietary and biliary cholesterol (Davis & Veltri, 2007). When combined with statins, ezetimibe provides additive LDL-C reductions (~15–20%) (Hammersley & Signy, 2017). The landmark IMPROVE-IT trial randomized high-risk post-MI patients with recent acute coronary syndrome to simvastatin 40 mg versus simvastatin 40 mg plus ezetimibe 10 mg daily (median follow-up 6 years) (Cannon et al., 2015). Combination therapy further reduced LDL-C (53.7 mg/dL vs 69.5 mg/dL; $p < 0.001$) and decreased major cardiovascular events at 7 years (absolute risk reduction 2.0%; HR: 0.936; 95% CI: 0.89–0.99) (Cannon et al., 2015). Subgroup analyses indicated greater benefit for patients with diabetes (5.5% absolute risk reduction; HR: 0.86) and for older adults aged ≥75 (HR: 0.80) highlighting ezetimibe's role in high-risk populations where further LDL-C lowering is required (Giugliano et al., 2018; Cannon et al., 2015). Meta-analyses of 27 trials (>21,000 participants) confirm that statin-ezetimibe combination therapy produces superior LDL-C reduction compared to statin monotherapy (mean additional reduction 15.1%) and maintains a favourable safety profile (Morrone et al., 2012).

PCSK9 inhibitors, including monoclonal antibodies evolocumab and alirocumab, preserve LDL receptor availability by preventing PCSK9-mediated receptor degradation, significantly enhancing hepatic LDL-C clearance (Jeswani et al., 2024). Clinical trials demonstrate 50–60% LDL-C reduction in patients with heterozygous FH, and reductions in major cardiovascular events of 15–20% (Tomlinson et al., 2021). For instance, the FOURIER trial reported a 59% LDL-C reduction with evolocumab, resulting in a 15% reduction in cardiovascular events; ODYSSEY Outcomes reported a 57% LDL-C reduction with alirocumab and a 15% reduction in adverse events (Jeswani et al., 2024). Inclisiran, a long-acting small interfering RNA (siRNA) targeting PCSK9, achieves similar LDL-C reductions (>50% for 6 months) with less frequent dosing (Jeswani et al., 2024). These therapies are generally well-tolerated, with injection site reactions being the most common adverse event (Jeswani et al., 2024).

Hormone replacement therapy (HRT) in postmenopausal women can partially restore premenopausal lipid profiles (Nie et al., 2022). Postmenopausal HRT has lipid-modifying effects by upregulating LDL receptors, enhancing HDL-C formation, and stimulating reverse cholesterol transport via ABCA1/ABCG1 transporters (Nie et al., 2022). A systematic review of 73 studies found that HRT significantly reduced LDL-C by 0.47 mmol/L (95% CI: −0.55 to −0.40), total cholesterol by 0.43 mmol/L, and Lp(a) by 49.46 mg/L relative to placebo (Nie et al., 2022). Moreover, the timing of HRT initiation relative to menopause is critical to its cardiovascular effects. Observational and trial data support a "timing hypothesis," whereby initiation within ten years of menopause may confer modest cardiovascular protection, whereas later initiation may increase risks of stroke or coronary events (Hodis & Mack, 2022). Novel pharmacologic approaches, including selective estrogen receptor modulators (SERMs) and tissue-selective estrogen complexes (TSECs), aim to replicate lipid benefits while minimizing systemic risks, though large-scale cardiovascular outcome data remain limited (Pickar et al., 2018). By selectively activating estrogen receptors in hepatic and vascular tissues while sparing breast and endometrial tissue, these agents aim to preserve favourable lipid profiles and reverse cholesterol transport without increasing oncologic risk (Martinkovich et al., 2014). Integration of these therapies with statins or PCSK9 inhibitors may offer synergistic LDL-C reduction in high-risk postmenopausal women, pending further study. Although HRT improves lipid profiles, its clinical use is constrained by increased risk of venous thromboembolism, stroke, and breast cancer, so it is typically reserved for symptomatic relief, with cardiovascular benefit considered secondary (Hodis & Mack, 2022).

In patients with severe or treatment-resistant dyslipidemia, particularly FH, lipoprotein apheresis provides immediate and potent LDL-C and Lp(a) reduction (Feingold, 2023). A multicenter study by von Dryander et al. demonstrated 55–70% reduction in LDL-C and Lp(a) per session. Corresponding reductions in cardiovascular event rates over two years were 54% for patients with isolated LDL elevation, 83% for elevated Lp(a), and 83.5% for combined LDL-C and Lp(a) elevations (von Dryander et al., 2013). Apheresis is intensive and

resource-demanding, but offers a life-saving intervention for patients who cannot achieve lipid targets pharmacologically (Lui et al., 2014).

Limitations and gaps, however, remain in sex-specific and longitudinal assessment. Women remain underrepresented in clinical trials, limiting precise understanding of HRT or statin efficacy across different life stages, particularly during postmenopause (Witting et al., 2022). Longitudinal studies tracking cumulative LDL-C from childhood into adulthood remain scarce, limiting the ability to quantify lifetime exposure and optimize the timing of therapy. Despite these challenges, evidence from RCTs and observational studies consistently demonstrates that aggressive LDL-C reduction, especially when initiated early, significantly decreases the risk of cardiovascular events and mitigates cumulative lipid burden; consequently both magnitude and duration of LDL-C exposure are further confirmed to be central determinants of cardiovascular outcomes.

A summary of the discussed therapies is presented in Table 2.

Therapy	Mechanism of Action	Key Efficacy Data	Notes
Statins	Inhibit HMG-CoA reductase → ↓ cholesterol synthesis → ↑ hepatic LDL receptors → ↑ LDL-C clearance	Pediatric FH: LDL-C ↓ 32% (29–35%), CIMT regression 0.01 mm, flow-mediated dilation ↑ 2.7%	Primary & secondary prevention; early initiation maximizes benefit; safe in children/adolescents
Ezetimibe	Inhibits NPC1L1 → ↓ intestinal cholesterol absorption → additive LDL-C reduction	LDL-C ↓ ~15–20% when combined with statin IMPROVE-IT: 7-year MACE 32.7% vs 34.7% (ARR 2%, HR 0.936), greater benefit in ≥75 years & diabetics	Adjunct to statin therapy, especially when target LDL-C not achieved with statins alone
PCSK9 inhibitors (Evolocumab, Alirocumab, Inclisiran)	Monoclonal antibodies or siRNA block PCSK9 → prevent LDL receptor degradation → ↑ LDL-C clearance	LDL-C ↓ 50–60% FOURIER: major CV events ↓ 15–20% ODYSSEY: LDL-C ↓ 57%, CV events ↓ 15%, safe & well-tolerated	FH, statin-intolerant, high-risk ASCVD; Inclisiran allows long-acting dosing (every 6 months)
Hormone Replacement Therapy (HRT)	Estrogen ↑ LDL receptors, ↑ HDL formation, ↑ reverse cholesterol transport (ABCA1/ABCG1)	LDL-C ↓ 0.47 mmol/L, total cholesterol ↓ 0.43 mmol/L, Lp(a) ↓ 49.46 mmol/L	Postmenopausal women; used mainly for symptomatic relief; cardiovascular benefits secondary due to risks (VTE, stroke, breast cancer)
Lipoprotein apheresis	Mechanical removal of LDL-C and Lp(a) from plasma	LDL-C & Lp(a) 55–70% per session 2-year CV event reductions: isolated LDL ↑ 54%, isolated Lp(a) ↑ 83%, combined ↑ 83.5%	Severe or treatment-resistant FH; homozygous FH; high Lp(a); resource-intensive but highly effective

Table 2. Therapeutic strategies targeting cumulative LDL-C exposure. Summary of lipid-lowering interventions, including statins, ezetimibe, PCSK9 inhibitors, hormone replacement therapy (HRT), and lipoprotein apheresis. The table highlights mechanisms of action, key efficacy data, relevant populations, and considerations.

Emerging sex-specific strategies for mitigating cumulative lipid burden

Beyond conventional lipid-lowering therapies, emerging sex-specific strategies increasingly emphasize the timing and biological context of LDL-C exposure rather than absolute cholesterol thresholds alone. Indeed, this paradigm shift is particularly relevant for women, whose cardiovascular risk is disproportionately influenced by biological differences in lipid metabolism, hormonal transitions, and lifetime exposure trajectories.

Early trajectory-based intervention in women

One promising approach involves the earlier identification of adverse lipid trajectories in premenopausal women, even when absolute LDL-C levels remain below traditional treatment thresholds (Roeters van Lennep et al., 2023). Women often experience prolonged periods of moderate hyperlipidemia before menopause, during which cumulative LDL-C exposure accumulates (Jeong & Kim, 2022). Incorporating trajectory-based or cholesterol-years modeling into risk assessment may therefore justify the earlier initiation of LDL-lowering therapy in select women, particularly those with additional risk modifiers such as family history, pregnancy-related dyslipidemia, or polycystic ovary syndrome (O'Kelly et al., 2022). Such strategies aim to prevent decades of unrecognized exposure that manifest as accelerated risk after menopause.

Targeting menopause as a critical inflection point

Menopause represents a biologically distinct window during which LDL-C levels rise sharply. Accordingly, emerging strategies emphasize proactive lipid monitoring and intervention during the perimenopausal transition, rather than delaying treatment until overt hypercholesterolemia or clinical events occur (Fasero & Coronado, 2025). This life-stage-specific approach aligns with cumulative risk models by prioritizing prevention at a point when lipid trajectories diverge most rapidly between sexes.

Addressing Lp(a) and genetically mediated risk

Sex-specific approaches may also be particularly relevant for Lp(a). Novel antisense oligonucleotides and siRNA therapies targeting LPA transcription offer the potential to reduce Lp(a) independently of LDL-C, addressing a component of cumulative lipid risk that is largely resistant to lifestyle modification and pharmacotherapy (Tselepis, 2023). These agents may be especially beneficial in women whose risk escalates after estrogen withdrawal makes clear genetically mediated lipid abnormalities.

Integration of cumulative lipid metrics into clinical practice

Finally, emerging strategies increasingly emphasize integration rather than new drugs alone, and evidence supports the clinical feasibility and utility of incorporating cumulative and longitudinal lipid exposure into cardiovascular risk prediction models. Traditional tools such as the Pooled Cohort Equations (PCE) rely on cross-sectional risk factor measurements and may therefore underestimate lifetime risk, particularly in individuals with prolonged moderate dyslipidemia or hormonally mediated lipid shifts (Yu et al., 2023). Recent work by Yu et al. demonstrates that integrating longitudinal risk factor data substantially improves ASCVD risk prediction beyond conventional approaches. In a multicohort study of over 15,000 individuals followed for adjudicated ASCVD events, a deep learning model incorporating eight years of longitudinal risk factor data outperformed the PCE in discrimination (AUROC 0.815 vs. 0.792) and calibration, with a net reclassification index of 0.385. Notably, model inputs mirrored routinely collected clinical variables, underscoring the practicality of longitudinal implementation within existing electronic health record infrastructures. These findings provide empirical support for cumulative lipid burden modeling and suggest that risk prediction

frameworks incorporating serial LDL-C exposure may more accurately capture lifetime atherogenic risk—particularly in women, whose cardiovascular risk trajectories are poorly reflected by single-point assessments. As longitudinal data capture becomes increasingly ubiquitous, integration of cumulative lipid metrics into risk calculators represents a scalable strategy to refine prevention and personalize lipid-lowering interventions across the lifespan.

4. Conclusion

Lipid metabolism is a central determinant of CVD, with cumulative exposure to atherogenic lipoproteins—particularly LDL-C—emerging as a more informative predictor of atherosclerotic burden than isolated midlife measurements. Epidemiological, genetic, and Mendelian-randomization studies consistently demonstrate that lifelong lower LDL-C, whether through inherited variants or early pharmacologic intervention, confers substantial and durable reductions in CHD risk. Sex-specific differences in lipid profiles, driven primarily by hormonal modulation, contribute to divergent CVD trajectories: men experience earlier elevations in LDL-C and greater early-life risk, whereas premenopausal women benefit from estrogen-mediated cardioprotection, which diminishes after menopause.

Importantly, empirical evidence supports the clinical relevance of assessing cumulative lipid exposure rather than relying solely on point-in-time measurements. Longitudinal analyses from the Framingham Offspring Cohort demonstrate that duration of moderate hyperlipidemia in early adulthood predicts future coronary heart disease in a dose-dependent manner, independent of contemporaneous lipid levels and traditional risk factors (Navar-Boggan et al., 2015). Notably, the majority of individuals with prolonged hyperlipidemia in early life would not have qualified for statin therapy under conventional 10-year risk-based guidelines, highlighting systematic underestimation of lifetime risk. Such findings emphasize the limitations of cross-sectional risk assessment and provide direct outcome-based support for cumulative lipid burden models.

Advances in data availability and analytic methods further corroborate the feasibility of translating lifetime lipid assessment into clinical practice. Recent work integrating longitudinal risk factor trajectories into deep learning–based prediction models demonstrate improved discrimination and risk reclassification for ASCVD compared with traditional pooled cohort equations (Yu et al., 2023). Because these models rely on routinely collected clinical variables, including serial cholesterol measurements, they offer a scalable framework for incorporating cumulative lipid exposure into individualized risk prediction. Together, these studies suggest that longitudinal lipid assessment can meaningfully improve risk stratification, particularly in populations whose lifetime risk is inadequately captured by conventional approaches.

Therapeutic interventions, including statins, ezetimibe, PCSK9 inhibitors, HRT, and lipoprotein apheresis, effectively target both the magnitude and duration of LDL-C exposure. Evidence highlights the importance of early initiation—particularly in high-risk populations such as children with FH—to reduce cumulative lipid burden and subsequent atherosclerotic events (van den Bosch et al., 2024). Despite such advancements, underrepresentation of women in clinical trials and limited longitudinal lipid-aging data remain key gaps, highlighting the need for sex-specific strategies and lifelong management approaches.

Collectively, these findings suggest a paradigm shift in cardiovascular prevention toward lifelong lipid management, emphasizing cumulative exposure rather than isolated thresholds. Incorporating longitudinal lipid trajectories into risk assessment frameworks has the potential to refine preventive strategies and advance precision medicine approaches tailored to sex, age, and lifetime CVD risk.

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Unfavourable Curves: Sex-Specific Lipid Metabolism and Lifelong Cardiovascular Risk

Abstract

Background: Dysregulated lipid metabolism, particularly elevated low-density lipoprotein cholesterol (LDL-C), is a major driver of ~~atherosclerosis as a subset of~~ cardiovascular disease (CVD). Sex differences in lipid biology and ~~the cumulative burden of LDL-~~cumulative LDL-C influence disease onset and severity, yet clinical practice often relies on single time-point measurements.

Methods: This review synthesizes evidence from 84 ~~epidemiological, genetic, and mechanistic~~ studies exploring lipid metabolism, sex-specific risk, cumulative LDL-C exposure, and the efficacy of ~~pharmacologic and~~ interventional therapies. Key studies of familial hypercholesterolemia (FH), longitudinal LDL-C trajectories, and major clinical trials of statins, ezetimibe, PCSK9 inhibitors, hormone replacement therapy (HRT), and lipoprotein apheresis were examined.

Results: Lifelong elevated LDL-C significantly increases CVD risk~~, with;~~ Mendelian-randomization analyses ~~indicating~~ indicate that early reductions confer a 3-fold greater benefit per unit LDL-C than interventions started later in life. ~~Men display higher early-life LDL-C and earlier onset of CVD, whereas premenopausal women benefit from estrogen-mediated lipid regulation, which diminishes post-menopause.~~ Statins~~, particularly when initiated early,~~ effectively lower LDL-C and reduce surrogate markers of atherosclerosis; combination therapy with ezetimibe or PCSK9 inhibitors provides additive benefits. HRT improves lipid profiles but carries cardiovascular and oncologic risks, limiting routine use. Lipoprotein apheresis offers substantial LDL-C and Lp(a) reduction in severe FH. Integration of cumulative lipid data into electronic health records and risk prediction models improves discrimination beyond traditional cross-sectional tools, with benefits for women whose risk trajectories are poorly represented by conventional methods.

Conclusions: ~~Both the magnitude and duration of LDL-C exposure are critical determinants~~Lifetime LDL-C exposure is a critical determinant of CVD risk. Early, ~~and~~ sustained intervention tailored to sex and individual risk optimizes prevention ~~and management~~. Translating cumulative lipid metrics into clinical practice offers a scalable approach to enhance risk stratification across the lifespan. Future research should address ~~longitudinal lipid trajectories,~~ sex-specific responses to therapy~~,~~ and integration of cumulative lipid metrics into clinical practice.

1. Introduction

The cardiovascular system sustains human life by maintaining the continuous circulation of oxygenated blood, nutrients, and metabolic substrates essential to systemic homeostasis; as a result, its failure—even transiently—carries severe physiological consequences (Chaudhry et al., 2022). Cardiovascular disease (CVD) encompasses a spectrum of disorders affecting the heart and its vasculature, most prominently coronary artery disease, cerebrovascular disease, and heart failure, and remains the leading global cause of death, accounting for approximately 17.9 million deaths annually or nearly one-third of all global mortality (Lopez et al., 2023; World Health Organization, 2019; Benjamin et al., 2018). It also constitutes an immense economic burden, generating an estimated $237 billion in indirect annual costs and is projected to exceed $368 billion by 2035 (Dunbar et al., 2018). Although the past half-century has seen remarkable advances in diagnostic imaging, pharmacological therapy, and surgical intervention that have improved acute outcomes, the overall prevalence of CVD continues to climb due to factors such as population aging, lifestyle-related risk factors, and widening health disparities (Zhou et al., 2022). The persistence of this burden thus highlights the need to interrogate the biological

determinants that shape cardiovascular risk longitudinally across the lifespan, rather than at isolated moments in time.~~.~~

Among these determinants, dysregulation of lipid metabolism has long been recognized as central to the pathogenesis of atherosclerotic disease (Steinbeck et al., 2025). Atherosclerosis—characterized by the accumulation of lipid-rich plaques within the arterial wall—develops gradually over decades and underlies most ischemic cardiovascular events (Pahwa & Jialal, 2023). While the cellular and molecular mechanisms governing plaque initiation and progression ~~have been~~are well-~~characterized~~established, with endothelial dysfunction, oxidative modification of low-density lipoprotein cholesterol (LDL-C) and chronic vascular inflammation primary among them, these processes ~~remain influenced by systemic metabolic and hormonal state~~are inherently time-dependent and modulated by systemic metabolic and hormonal states~~s~~ (Popa-Fotea et al., 2023). Consequently, lipid metabolism serves as both a mechanistic and epidemiological bridge between molecular pathophysiology and population-level ~~disease~~ CVD risk.

The risk of CVD demonstrates marked demographic heterogeneity. Men generally exhibit a higher incidence at younger ages, whereas the risk for women increases sharply following the onset of menopause, narrowing the sex gap in later decades (Merz & Cheng, 2016). The mechanistic basis of this disparity remains incompletely understood, though converging evidence implicates differences in lipid metabolism as a major driver (Robinson et al., 2022). ~~Estrogen exerts multiple cardioprotective effects, including enhanced hepatic clearance of LDL-C and increased high-density lipoprotein cholesterol (HDL-C) levels, which mediate reverse cholesterol transport~~Estrogen-mediated lipid regulation, characterized by enhanced hepatic LDL clearance and increased high-density lipoprotein cholesterol (HDL-C), is thought to contribute to the relative cardioprotection observed in premenopausal women (Palmisano et al., 2017). ~~The decline in circulating estrogen after menopause attenuates these protective mechanisms, contributing to unfavourable shifts in lipid profiles and narrowing the sex gap in CVD risk during later adulthood~~The postmenopausal decline in estrogen attenuates these effects, leading to adverse lipid shifts and accelerated atherosclerotic risk (Raj et al., 2023). By contrast, men, lacking this hormonal modulation, exhibit elevated LDL-C and reduced HDL-C levels throughout life, consistent with their earlier disease onset (Pérez-López et al., 2010). Although these sex differences are well-documented, their interaction with *lifelong* lipid exposure remains insufficiently characterized.

Cardiovascular risk is shaped not only by absolute lipid concentrations at a single point in time, but by cumulative exposure to atherogenic lipoproteins across the lifespan. Sex-specific lipid trajectories, particularly those shaped by hormonal transitions, may therefore exert disproportionate influence on lifetime cardiovascular risk that is not captured by conventional point-based risk estimates. Indeed, current clinical risk assessment frameworks rely predominantly on single time-point lipid measurements, which may inadequately capture the cumulative nature of atherogenic exposure. Such approaches can underestimate early-life risk, misclassify individuals with historically elevated cholesterol but later treatment, and obscure sex-specific trajectories shaped by hormonal transitions~~Despite the well-established association between serum cholesterol and CVD, the relationship between lipid metabolism, sex, and aging remains incompletely defined. Much of the epidemiological literature has emphasized static lipid measurements rather than the cumulative exposure to atherogenic lipoproteins over time—a factor that may more accurately capture lifelong cardiovascular risk~~ (Zhang et al., 2021~~). Moreover, sex-specific variations in hormonal milieu, hepatic lipid regulation, and lipoprotein turnover complicate traditional interpretations of cholesterol as a uniform biomarker (~~; Seidemann et al., 2024). ~~These considerations have prompted the examination of cholesterol as a dynamic indicator of metabolic aging and hormonal influence~~.Emerging evidence from Mendelian randomization studies and longitudinal cohorts suggests that the *duration* and *timing* of LDL-C exposure, rather than isolated values, are critical determinants of cardiovascular outcomes, with early reductions conferring disproportionately greater benefit than later intervention.

In this context, cumulative lipid burden may be conceptualized as the time-integrated exposure to circulating atherogenic lipoproteins, operationalized through metrics such as “cholesterol-years” or LDL years, serial aggregation of repeated lipid measurements, or genetic proxies for lifelong LDL-C elevation. However, the clinical implementation of such frameworks remains limited, and sex-specific validation is notably sparse.

~~Consequently~~Accordingly, this literature review synthesizes current evidence ~~on cholesterol as a risk factor for CVD and sex differences in lipid profiles to examine cholesterol levels relative to age as a proxy for cumulative lipid burden across the lifespan.~~ to evaluate cumulative lipid exposure as a determinant of cardiovascular risk across the lifespan, with particular attention to sex-specific biology. Rather than re-establishing known sex differences in lipid profiles, this review critically examines how cumulative LDL-C burden has been measured, where empirical support exists, and where significant gaps, especially regarding sex-stratified risk estimation, persist~~We examine whether this index exhibits sex-specific associations with CVD risk and whether cumulative lipid exposure, mediated by hormonal and metabolic factors, partially explains the demographic patterns observed in disease incidence~~. By integrating mechanistic insights with epidemiological data, this review aims to clarify the translational potential of cumulative lipid metrics and to identify key methodological and evidentiary barriers that must be addressed to advance sex-specific cardiovascular prevention strategies. ~~how cumulative lipid burden and hormonal regulation jointly shape the pathophysiology of CVD, and to identify critical gaps in understanding that impede the knowledge of sex-specific preventive and therapeutic strategies.~~

2. Methods

Literature search strategy

A structured literature search was conducted to identify peer-reviewed studies examining the relationship between lipid metabolism, cholesterol regulation, sex-specific biological differences, and CVD risk. The primary database used was PubMed, with supplementary searches performed in Scopus and Google Scholar to ensure comprehensive coverage of both biomedical and biochemical research. The search encompassed publications available in English up to October 2025.

Search terms included, but were not limited to, combinations of the following keywords and Boolean operators: “cardiovascular disease” OR “atherosclerosis” AND “cholesterol” OR “lipids” OR “lipid metabolism” AND “sex differences” OR “gender differences” OR “menopause” OR “estrogen”. Additional terms such as “hormonal regulation”, “LDL-C”, “HDL-C”, “reverse cholesterol transport”, and “cumulative lipid burden” were incorporated in secondary searches to refine topic specificity. Reference lists of major reviews and landmark cohort studies were also manually screened to capture relevant primary research not indexed under these search terms.

Inclusion and exclusion criteria

Studies were selected based on predefined inclusion and exclusion criteria. Eligible studies ~~included the following~~met one or more of the following criteria: ~~: recent review articles (cutoff: within the past 50 years) providing comprehensive analyses of lipid metabolism in CVD; large-scale epidemiological or cohort studies that examined serum lipid levels, aging, and cardiovascular outcomes in male and female populations; and mechanistic or biochemical studies clarifying the molecular pathways by which sex hormones, particularly estrogen, influence lipoprotein metabolism and atherogenesis.~~large-scale epidemiological or longitudinal cohort studies examining serum lipid levels, aging, and cardiovascular outcomes in human populations; genetic or Mendelian randomization studies evaluating lifelong exposure and cardiovascular risk; mechanistic or biochemical studies elucidating pathways by which sex hormones influence lipid metabolism and atherogenesis; and review articles synthesizing lipid metabolism and CVD risk, included to contextualize primary findings.

~~Exclusion criteria comprised~~Studies were excluded if they were non-peer-reviewed sources, case reports, editorials, or conference abstracts; focused exclusively on animal ~~studies~~ or in vitro models without clear translational relevance to human lipid metabolism; or~~, and studies focusing exclusively on~~addressed ~~unrelated~~ metabolic disorders ~~unless directly connected~~unrelated to cardiovascular lipid metabolism.

Screening and data extraction

The literature search yielded approximately 1,200 records across all databases. After removal of duplicates (~200), ~1000 records underwent title and abstract screening. Of these, ~850 articles were excluded based on relevance, leaving ~150 full-text articles assessed for eligibility. Following full-text review, 84 articles met inclusion criteria and were incorporated into the final qualitative synthesis.

Screening, eligibility assessment, and data extraction were performed by the author. Extracted data included study design, population characteristics, lipid metrics assessed (e.g., point-based LDL-C versus cumulative measures), duration of follow-up, sex-stratified analyses, and reported cardiovascular outcomes.

A PRISMA flow diagram summarizing the study selection process is provided in Figure 1.

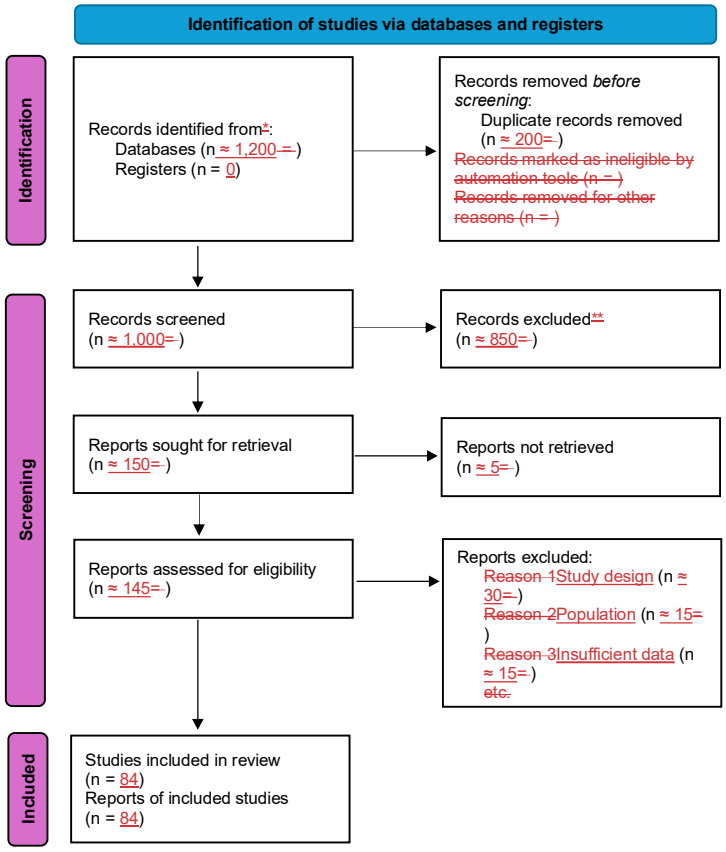

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Figure 1. PRISMA flow diagram summarizing the literature search and study selection process. The literature search yielded approximately 1,200 records across databases, with ~200 duplicates removed. Title and abstract screening excluded ~850 articles, and 150 full-text articles were assessed for eligibility. Following full-text review, 84 studies were included in the final qualitative synthesis.

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Synthesis strategy

Included studies were grouped thematically according to whether they employed traditional point-based lipid measurements or cumulative lipid exposure metrics. Within these groups, evidence was further synthesized based on sex-specific analyses, age-related lipid trajectories, and cardiovascular outcomes. This approach enabled a direct comparison between conventional risk paradigms and emerging cumulative exposure frameworks.

3. Results

Collectively, lipid biology is both a causal and modulatory factor in cardiovascular disease. Understanding how lipids circulate, modify, and accumulate within arterial walls is essential to contextualize both epidemiological trends and sex-based disparities in disease burden. Beyond the absolute concentrations of circulating lipoproteins, the cumulative exposure to atherogenic lipids over the lifespan is a central determinant of disease trajectory. This passage provides the biochemical context for understanding sex- and age-related heterogeneity in cardiovascular risk, which will be explored in greater depth in subsequent sections.

~~Pathology and lipid metabolism~~Lipid-driven atherosclerosis as a cumulative process

Lipid metabolism is central to the etiology of CVD, primarily through its influence on atherosclerotic plaque formation and progression. Atherosclerosis, the predominant pathological substrate underlying most ischemic cardiovascular events, is a progressive process initiated by endothelial dysfunction, in which the vascular endothelium loses its ability to regulate vascular tone and maintain barrier integrity (Park & Park, 2015). This impairment facilitates the subendothelial retention of apolipoprotein B-containing lipoproteins, primarily low-density lipoprotein cholesterol (LDL-C), which represents the principal atherogenic lipoprotein species (Tabas et al., 2007).

Upon infiltration into the arterial intima, LDL particles undergo oxidative and enzymatic modifications, producing oxidized LDL (oxLDL) (Jiang et al., 2022). OxLDL has multiple atherogenic properties, including upregulation of endothelial cell adhesion molecules, recruitment of circulating monocytes, and induction of pro-inflammatory signaling cascades (Poznyak et al., 2021). Monocytes differentiate into macrophages within the intima, engulfing oxLDL via scavenger receptors, and as lipid accumulation exceeds cellular processing capacity, macrophages transform into foam cells and form the fatty streak—the earliest visible lesion of atherosclerosis (Chistiakov et al., 2016; Ouyang et al., 2023).

Over time, smooth muscle cells migrate into the intima and deposit extracellular matrix, creating a fibrous cap over a lipid-rich necrotic core (Harman & Jørgensen, 2019). This plaque can remain stable for years, but oxidative stress and inflammatory activity promote thinning of the fibrous cap, increasing the likelihood of rupture, which subsequently exposes thrombogenic contents to circulating blood and precipitates acute coronary syndromes such as MI (Loftus, 2011). This process is thus inherently time dependent. More specifically, LDL particles that circulate for longer periods are more likely to undergo oxidative modification and arterial retention, increasing plaque burden incrementally over decades (Akyol et al., 2025). Consequently, atherosclerosis is fundamentally cumulative, with lifetime exposure to atherogenic lipoproteins representing a key determinant of disease severity (Almohtasib et al., 2024). Atherosclerosis thus reflects both the magnitude and duration of LDL-C exposure, supporting a cumulative exposure or a “cholesterol-years” model of

development. This framework provides the mechanistic foundation for interpreting sex- and age-related heterogeneity in cardiovascular risk.

Figure 2 provides a schematic overview of the molecular pathways governing lipid metabolism.

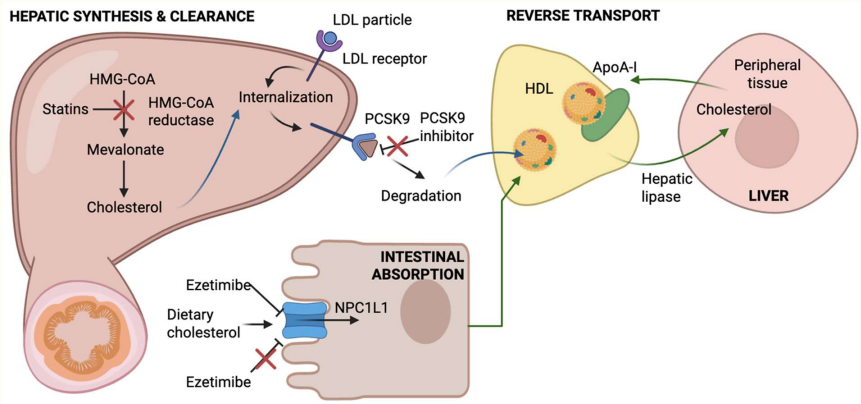

Figure 2. Molecular mechanisms of lipid metabolism and therapeutic intervention points. Simplified schematic illustrating hepatic cholesterol synthesis, intestinal absorption, LDL receptor-mediated clearance, and reverse cholesterol transport, highlighting targets of statins, ezetimibe, PCSK9 inhibitors, and hormone-mediated regulation.

The interactions between lipid species further modulate atherosclerotic risk. While LDL-C contributes directly to plaque formation, high-density lipoprotein cholesterol (HDL-C) mediates protective mechanisms through reverse cholesterol transport, whereby excess cholesterol is effluxed from peripheral tissues and transported to the liver for excretion (Ouimet et al., 2019).

~~Sex hormones exert a considerable regulatory effect on lipid metabolism, contributing to observed demographic patterns in CVD incidence (Robinson et al., 2022). Estrogen upregulates hepatic LDL receptor expression, increasing clearance of circulating LDL particles and thereby lowering serum LDL-C (Palmisano et al., 2017). Concurrently, estrogen also increases HDL-C levels, which promotes reverse cholesterol transport (Palmisano et al., 2017). These combined mechanisms confer a premenopausal cardioprotective lipid profile in women (Ryczkowska et al., 2022). Following menopause, declining estrogen levels attenuate these protective mechanisms; LDL-C increases, HDL-C decreases, and women's cardiovascular risk rises sharply (Ryczkowska et al., 2022). By contrast, men lack this hormonal protection throughout life, which may explain their earlier onset of CVD (Rodgers et al., 2019).~~

Sex-specific lipid ~~profiles~~trajectories across the lifespan

Epidemiological data consistently demonstrate pronounced sex-based differences in both lipid metabolism and cardiovascular risk trajectories. Men generally exhibit higher LDL-C and triglyceride concentrations, coupled with lower HDL-C levels, beginning as early as adolescence (Russo et al., 2015). These differences correlate with earlier onset and greater lifetime incidence of atherosclerotic CVD (Rodgers et al., 2019). In contrast, premenopausal women typically maintain a more favourable lipid profile, characterized by lower LDL-C and

elevated HDL-C levels, which correspond to their reduced risk of coronary events prior to menopause (Ryczkowska et al., 2022).

Figure 3 illustrates longitudinal lipid trajectories for men and women across adulthood.

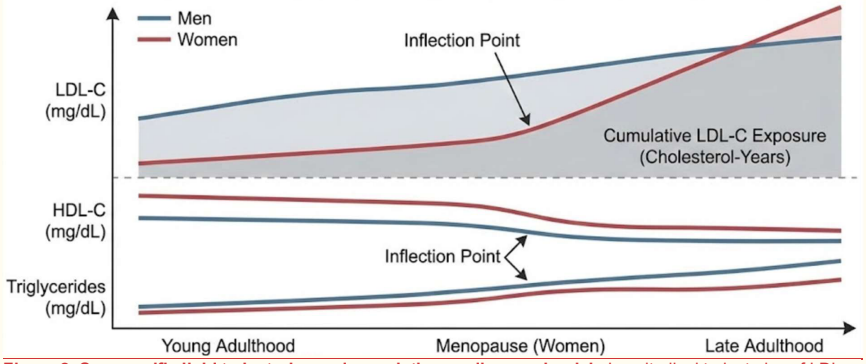

Figure 2. Sex-specific lipid trajectories and cumulative cardiovascular risk. Longitudinal trajectories of LDL-C, HDL-C, and triglycerides in men and women across adulthood. Inflection points highlight the midlife rise in LDL-C among women during the menopausal transition. Shaded areas indicate cumulative LDL exposure ("cholesterol-years"), illustrating differences in lifetime atherogenic burden and periods of elevated cardiovascular risk.

This divergence is largely attributed to the hormonal regulation of hepatic lipid processing. Androgen-dominant metabolic environments in males promote increased hepatic lipase activity, accelerating HDL catabolism and reducing HDL-C concentration (Herbst et al., 2003). Concurrently, reduced LDL receptor density in hepatocytes contributes to slower LDL clearance from the circulation; these features collectively produce an early-life metabolic phenotype conducive to lipid retention and vascular injury (Pirahanchi et al., 2023).

Sex hormones exert a considerable regulatory effect on lipid metabolism, contributing to observed demographic patterns in CVD incidence (Robinson et al., 2022). The onset of menopause represents a pivotal inflection point in female lipid physiology. Estrogen—the principal modulator of lipid homeostasis in women—exerts multifaceted effects on lipoprotein mechanisms, upregulating hepatic LDL receptor expression, facilitating LDL particle uptake and degradation, and promoting apolipoprotein A-I (ApoA-I) synthesis, the major protein constituent of HDL (Nii et al., 2016; Palmisano et al., 2018). These combined mechanisms confer a premenopausal cardioprotective lipid profile in women (Ryczkowska et al., 2022). Following menopause, declining estrogen levels attenuate these protective mechanisms; LDL-C increases, HDL-C decreases, and women's cardiovascular risk rises sharply (Ryczkowska et al., 2022). By contrast, men lack this hormonal protection throughout life, which may explain their earlier onset of CVD (Rodgers et al., 2019). Moreover, estrogen stimulates the activity of ATP-binding cassette transporters (ABCA1 and ABCG1) involved in cholesterol efflux, thereby augmenting reverse cholesterol transport (Bao et al., 2023). These hormonal transitions shift women from a low cumulative LDL exposure trajectory toward a rapidly accelerating risk profile in midlife, narrowing the sex gap in atherosclerotic cardiovascular disease (ASCVD incidence.

Beyond circulating estrogen, sex-specific lipid metabolism is modulated by androgens and progesterone. Androgens, which predominate in males, exert multiple pro-atherogenic effects, primarily through hepatic lipid regulation (Xu et al., 2022). Elevated androgens increase hepatic lipase activity, accelerating the catabolism of HDL particles and leading to smaller, less functional HDL that is less effective in reverse cholesterol transport (Kantor et al., 1985). Additionally, androgen exposure favors the production of small, dense LDL particles, which

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are more susceptible to oxidation, exhibit increased arterial retention, and undergo atherogenic modification (Vekic et al., 2022). These molecular and structural alterations provide a mechanistic basis for the higher prevalence of early-onset cardiovascular disease observed in males.

In contrast, progesterone, a dominant female sex hormone during the luteal phase and pregnancy, influences lipid metabolism in a more nuanced manner. Progesterone modulates HDL functionality by altering particle composition and may affect the distribution of LDL subfractions, though the net cardiovascular impact remains less clearly defined (Corsini et al., 1988). Importantly, these effects are context-dependent, influenced by hormonal milieu, age, and concomitant estrogen exposure. Estrogen receptor signaling, mediated by ERα and ERβ, plays a pivotal role in hepatocyte lipid handling, regulating transcription of key genes including LDL receptor, apolipoprotein A-I, and enzymes involved in cholesterol esterification and bile acid synthesis (Zhu et al., 2018). Additionally, estrogen modulates sterol regulatory element-binding protein (SREBP) pathways, which are central to endogenous cholesterol synthesis and intracellular lipid homeostasis (Sakai & Rawson, 2001). Collectively, these hormonal and intracellular mechanisms underlie the observed divergence in lipid profiles between males and females across the lifespan, contributing to delayed atherosclerotic development in premenopausal women and accelerated risk in men and postmenopausal women.

The effects of sex hormones extend beyond circulating lipoproteins to cellular processes in the vascular wall. Estrogen enhances endothelial nitric oxide synthase (eNOS) activity, promoting vasodilation and reducing oxidative stress, while androgens may favor pro-inflammatory cytokine expression and endothelial dysfunction (MacRitchie et al., 1997). These vascular effects amplify the consequences of sex-specific lipid profiles, reinforcing the higher baseline risk of atherogenesis in males and the protective effect of premenopausal estrogen in females.

In addition to conventional lipid fractions, lipoprotein(a) (Lp(a)) represents a genetically determined, highly atherogenic lipoprotein whose plasma concentration is largely stable throughout life and minimally influenced by diet, exercise, or conventional lipid-lowering therapies (Farzam et al., 2024). Structurally, Lp(a) consists of an LDL-like particle covalently bound to apolipoprotein(a), a glycoprotein homologous to plasminogen, which confers prothrombotic properties in addition to its atherogenic potential (Farzam et al., 2024). Elevated Lp(a) levels have been associated with accelerated coronary artery disease, calcific aortic valve disease, and heightened inflammatory signaling in the vascular endothelium (Wambua et al., 2025).

The clinical impact of Lp(a) appears to differ by sex and hormonal status. In premenopausal women, Lp(a)-related risk is partially mitigated by estrogen-mediated enhancement of LDL receptor expression and lipoprotein clearance (Corral et al., 2024). Postmenopausal women, however, experience a disproportionate increase in atherosclerotic cardiovascular disease (ASCVD) risk when Lp(a) levels are elevated, potentially due to the combined effects of increased LDL-C, loss of estrogen-driven hepatic clearance, and heightened inflammatory susceptibility in the vascular wall (Roeters van Lennep et al., 2023).

Consequently, these well-established sex differences have been reframed as divergent cumulative exposure trajectories shaped by hormonally timed inflection points rather than as static biological distinctions. Recent longitudinal analyses emphasize that cardiovascular risk divergence arises from differences in *when* and *for how long* individuals are exposed to atherogenic lipid environments, rather than from fixed sex-based lipid set points (Wilkins et al., 2024; Zheutlin et al., 2025). This temporal reframing has shifted the field away from cross-sectional lipid comparisons toward life-course modeling approaches that better capture the delayed but accelerated risk observed in postmenopausal women. Such findings highlight the need to integrate sex, age, and duration of exposure into cardiovascular risk assessment rather than treating sex differences as isolated phenomena.

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Longitudinal evidence of cumulative lipid burden

As endogenous estrogen production declines during the menopausal transition, these regulatory mechanisms wane, leading to measurable alterations in serum lipid composition (Patel et al., 2025). The extent and timing of these changes have been captured through large-scale prospective cohorts, including the Framingham

Offspring Study (FOS) and the Study of Women's Health Across the Nation (SWAN) (Duncan et al., 2019; El Khoudary et al., 2019). More specifically, these cohorts provide empirical support for cumulative lipid exposure as a superior predictor of cardiovascular outcomes compared with single-point LDL measurements.

FOS, a longitudinal cohort initiated in 1971 to follow the descendants of the original Framingham Heart Study participants, provides some of the most comprehensive sex-stratified analyses of lipid trajectories and cardiovascular outcomes. Among 3,875 participants (54% women; mean age 48 years) followed between 1979 and 2014, investigators identified five distinct trajectories of total cholesterol (TC), LDL-C, and HDL-C across adulthood (Duncan et al., 2019). Importantly, w~~W~~omen exhibited marked inflection points in LDL-C and HDL-C levels during midlife, consistent with the perimenopausal transition, where average LDL-C concentrations increased by approximately 10–15%, while HDL-C declined modestly—changes that paralleled reductions in circulating estradiol rather than chronological aging or body mass index (Ryczkowska et al., 2022). This finding reinforces that timing and duration of exposure, rather than absolute midlife LDL-C alone, drive long-term risk.

Elevated lipid trajectories were strongly associated with future ~~atherosclerotic cardiovascular disease (~~ASCVD~~)~~ and mortality. Participants maintaining LDL-C >155 mg/dL, TC >240 mg/dL, or non-HDL-C >180 mg/dL had over a twofold increase in ASCVD and all-cause mortality risk compared with those maintaining optimal lipid levels (HR_{ascvd} = 5.09 [95% CI: 1.54–16.85]; HR_{death} = 4.04 [1.84–8.89]) (Duncan et al., 2019). Conversely, persistently low HDL-C (<40 mg/dL) was associated with a nearly 4-fold higher ASCVD risk compared with concentrations >70 mg/dL (Duncan et al., 2019). These findings reinforce the concept of cholesterol-years—that is, cumulative exposure to atherogenic lipoproteins—as a more precise determinant of lifetime cardiovascular risk than any single lipid measurement (Wilkins et al., 2024). From a mechanistic perspective, these observations align with the decline in hepatic LDL receptor expression post-menopause, leading to reduced LDL clearance and prolonged lipoprotein residence time within circulation, thereby increasing the probability of oxidative modification and endothelial retention (P, 2025). FOS thus provides population-scale confirmation of the biochemical mechanisms previously discussed.

Complementing the Framingham data, SWAN—a multi-ethnic, prospective cohort initiated in 1994—has characterized the dynamic lipid changes across the menopausal transition in greater temporal ~~resolution~~resolution and demonstrated that the steepest increases in LDL-C occurred within a narrow window surrounding the final menstrual period, temporally aligned with estradiol decline. ~~.~~SWAN followed over 3,000 premenopausal women aged 42-52 from diverse ethnic backgrounds (Caucasian, African-American, Chinese, Japanese, and Hispanic) for over two decades, incorporating both hormonal and metabolic assessments at annual intervals (El Khoudary et al., 2019; Derby et al., 2009). Longitudinal analyses across the menopausal stages revealed that the steepest rise in LDL-C and total cholesterol levels occurred within a two-year window surrounding the final menstrual period (FMP), temporally coinciding with the estradiol nadir (El Khoudary et al., 2021). These changes were most pronounced during early postmenopause, when estrogen depletion accelerates hepatic lipid remodeling (El Khoudary et al., 2021).

Mechanistically, SWAN's metabolic substudy highlighted that declining estrogen levels were associated with increased hepatic lipase activity and reduced ApoA-I concentrations, attenuating HDL particle maturation and impairing reverse cholesterol transport (Woodard et al., 2011). Additionally, small dense LDL particles became increasingly prevalent in the years following menopause, a pattern associated with heightened atherogenic potential due to their greater arterial wall penetrance and oxidative susceptibility (He et al., 2025). Importantly, SWAN's findings highlight menopause as a biologically discrete period of accelerated lipid remodeling that materially contributes to cumulative atherogenic burden.

Taken together, the Framingham and SWAN cohorts provide converging evidence that the menopausal transition represents a biologically distinct period of lipid remodeling with direct implications for cardiovascular risk. Framingham emphasizes the cumulative, long-term impacts of rising LDL-C post-menopause on clinical outcomes, while SWAN delineates the temporal and mechanistic sequence of lipid alterations accompanying hormonal ~~delines~~declines; its inclusion of diverse populations underscores that, while hormonal decline is universal, its phenotypic lipid effects are modulated by race, diet, and genetic background.

Beyond circulating estrogen, sex-specific lipid metabolism is modulated by androgens and progesterone. Androgens, which predominate in males, exert multiple pro-atherogenic effects, primarily through hepatic lipid regulation (Xu et al., 2022). Elevated androgens increase hepatic lipase activity, accelerating the catabolism of HDL particles and leading to smaller, less functional HDL that is less effective in reverse cholesterol transport (Kantor et al., 1985). Additionally, androgen exposure favors the production of small, dense LDL particles, which are more susceptible to oxidation, exhibit increased arterial retention, and undergo atherogenic modification (Vekic et al., 2022). These molecular and structural alterations provide a mechanistic basis for the higher prevalence of early-onset cardiovascular disease observed in males.

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When contextualized within the broader framework of lipid biology, these findings reinforce the notion that lifetime exposure to atherogenic lipoproteins—modulated by the hormonal milieu—is a principal determinant of CVD onset and severity. This cumulative exposure framework integrates both male and female trajectories: men experience a steady accrual of risk beginning early in adulthood due to persistently higher LDL-C levels, whereas women's risk accelerates sharply post-menopause as estrogen-mediated lipid regulation deteriorates. Such evidence provides a mechanistic and epidemiological rationale for sex-specific therapeutic approaches, discussed in subsequent sections, emphasizing the potential for early lipid intervention in premenopausal women to mitigate post-menopausal risk acceleration.

~~Cumulative lipid burden and aging~~Empirical support for the cholesterol-years model

The primary aim of this review is to evaluate empirical evidence supporting cumulative lipid exposure models and to examine whether these approaches reveal sex-specific associations with cardiovascular outcomes beyond conventional point-based measurements. While relatively few studies explicitly operationalize cumulative cholesterol metrics, a growing body of longitudinal, genetic, and cohort-based evidence demonstrates that duration- and burden-based lipid exposure more accurately predicts cardiovascular risk, particularly when sex- and life-stage–specific trajectories are considered.

Indeed, w~~W~~hile acute lipid measurements are standard clinical practice, growing evidence emphasizes that cumulative exposure to atherogenic lipoproteins, rather than isolated LDL-C levels, is the principal determinant of CVD risk (Zheutlin et al., 2025). Prolonged circulation of LDL particles increases the probability of their oxidative modification and subsequent arterial retention, accelerating atherogenesis (Maiolino et al., 2013). Indeed, accumulating epidemiological and genetic evidence supports a *cholesterol-years* model of atherogenesis in which the duration of exposure to atherogenic lipoproteins materially influences lifetime risk of coronary heart disease (CHD) (Zheutlin et al., 2025). In other words, genetic and modeling studies provide direct evidence that cumulative LDL exposure predicts cardiovascular outcomes more accurately than conventional point-based metrics.

Operationally, cumulative LDL exposure ("cholesterol-years") is calculated by aggregating serial LDL-C measurements over time, typically as the area under the LDL-C–time curve or as a time-weighted average of repeated values across adulthood (Ference et al., 2012). In genetic studies, this exposure is approximated through lifelong LDL-C differences conferred by specific variants, providing a proxy for sustained exposure independent of treatment or behaviour (Ference et al., 2012). In observational cohorts, cumulative burden has been modeled using repeated laboratory measurements collected at regular intervals, enabling estimation of total LDL exposure across decades (Zhang et al., 2021).

Mendelian-randomization meta-analyses by Ference et al. provide strong support for the cholesterol-years paradigm. Ference et al. integrated nonoverlapping data from 312,321 participants across nine polymorphisms affecting LDL-C regulation. Each mmol/L genetically lower LDL-C was associated with a 54.5% reduction in CHD risk (95% CI: 48.8–59.5%), reflecting a ~3-fold greater risk reduction per unit LDL-C than statin therapy initiated later in life ($p = 8.43 \times 10^{-9}$) (Ference et al., 2012). These results demonstrate that early and sustained reductions in LDL-C produce disproportionately larger cardiovascular benefits, supporting the notion that cumulative LDL exposure, rather than cross-sectional levels alone, governs atherosclerotic progression. Conceptually, these observations have been framed as the cholesterol-years or lifelong exposure model: the findings strongly support an area-under-the-curve model of LDL exposure ~~area under the LDL-C curve~~ across the lifespan that appears to predict disease more accurately than a single midlife measurement (Ference et al., 2012).

Complementing genetic findings, population-level analyses further corroborate this framework. Zhang et al. 2021 pooled data from four prospective cohorts (18,288 participants; 56.4% women; mean age 56.4 ± 3.7 years; median follow-up ≈ 16 years) (Zhang et al., 2021). Using cumulative LDL-C, time-weighted average (TWA), and LDL-C slope metrics, the study found that both cumulative LDL-C and TWA LDL-C were independently associated with incident CHD even after adjustment for the most recent midlife LDL-C and traditional CVD risk factors (Zhang et al., 2021). By contrast, the LDL-C slope alone was not significantly associated with CHD after accounting for midlife levels, reinforcing that the area *under the LDL curve* (cumulative burden) rather than transient changes in LDL-C is the critical metric (Zhang et al., 2021). Thus a lifelong lipid exposure model is translationally relevant once mechanistic insights from genetic studies are extended into population-level observations.

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Navar-Boggan et al. provide some of the strongest longitudinal evidence that cumulative lipid exposure predicts cardiovascular outcomes more accurately than single time-point lipid measurements. Using data from the Framingham Offspring Cohort, the authors examined 1,478 adults free of cardiovascular disease through age 55 and quantified duration of moderate hyperlipidemia in early adulthood (defined as non-HDL cholesterol ≥160 mg/dL). Over a median 15-year follow-up, CHD incidence increased in a clear dose-dependent manner with longer cumulative exposure: 4.4% among individuals with no exposure, 8.1% among those with 1-10 years of exposure, and 16.5% among those with 11-20 years of exposure ($P < 0.001$) (Navar-Boggan et al., 2015). Importantly, this association persisted after adjustment for contemporaneous lipid levels at age 55 and other cardiovascular risk factors, with a 39% increase in CHD risk per decade of hyperlipidemia exposure (HR 1.39; 95% CI 1.05-1.85) (Navar-Boggan et al., 2015). Notably, 85% of participants with prolonged hyperlipidemia would not have met statin treatment thresholds under contemporary 10-year risk-based guidelines, highlighting systematic underestimation of early-life risk (Navar-Boggan et al., 2015). Even among individuals not considered statin candidates at age 55, cumulative exposure remained independently associated with future CHD (adjusted HR 1.67; 95% CI 1.06-2.64) (Navar-Boggan et al., 2015). These findings demonstrate that cumulative lipid burden captures clinically meaningful risk missed by point-in-time lipid measurements and provide direct empirical support for lifetime exposure models of atherosclerotic risk. Although Navar-Boggan et al. did not stratify outcomes by sex, the findings are particularly salient when interpreted alongside sex-specific lipid trajectories observed in Framingham and SWAN, where women experience delayed but accelerated LDL accumulation post-menopause. Together, these studies suggest that cumulative lipid exposure may systematically underestimate risk in women when assessed using midlife point measurements alone.

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Further evidence comes from the Copenhagen General Population Study (CGPS) which enrolled 91,131 individuals between 2003 and 2015, with a mean follow-up of 7.7 years (Mortensen & Nordestgaard, 2020). During this period, 1,515 first myocardial infarctions (MI) and 3,389 atherosclerotic cardiovascular events occurred, where each 1.0 mmol/L increase in LDL-C was associated with a 34% higher risk of MI (HR: 1.34; 95% CI: 1.27–1.41) and a 16% higher risk of ASCVD overall (HR: 1.16; 95% CI: 1.12–1.21) (Mortensen & Nordestgaard, 2020). Notably, risk was amplified in older adults (aged 70–100 years) and in individuals with very high LDL-C (≥5.0 mmol/L), consistent with the notion that both absolute levels and cumulative exposure exacerbate atherosclerotic outcomes (Mortensen & Nordestgaard, 2020). Notably, the CGPS relies on single-point LDL-C measurements, which limits its ability to directly assess cumulative lipid exposure. However, its findings nevertheless align with cumulative risk models by demonstrating amplified risk at older ages, when lifetime LDL burden is greatest, but highlight the need for studies incorporating repeated measurements to more accurately quantify exposure over time.

Complementing these observational studies, population screening for heterozygous familial hypercholesterolemia (FH) demonstrates the extreme consequences of lifelong elevated LDL-C. FH, an autosomal dominant genetic disorder caused by mutations in genes critical for LDL clearance that impair hepatic LDL uptake, is characterized by markedly elevated plasma LDL-C concentrations from birth (Warden et al., 2024). Prevalence estimates range from 1/500 to 1/200 in Northern European populations, yet <1% of affected individuals are diagnosed in most countries (Nordestgaard et al., 2013). Individuals with untreated FH experience up to a 13-fold increased risk of CHD, suggesting that prolonged and substantial elevations in LDL-C from early life dramatically accelerate atherosclerosis (Nordestgaard et al., 2013). FH thus provides an application of the cholesterol-years paradigm: both the magnitude and duration of LDL-C elevation are critical determinants of cardiovascular risk, and the findings reinforce the mechanistic link between lifelong LDL burden and atherosclerotic disease.

Collectively, converging evidence from genetic, longitudinal, and clinical studies emphasizes that cardiovascular risk is not merely a function of LDL-C concentration at a single point in time, but rather of its cumulative exposure across the lifespan. Thus, early and sustained lipid control, rather than reactive prevention in midlife, yields disproportionately greater protection against lifetime cardiovascular risk. Table 1 synthesizes key studies comparing hookup between cumulative LDL metrics and traditional point-based measurements, illustrating the relative paucity but growing importance of longitudinal exposure modeling in cardiovascular risk assessment.

Study	Population	LDL Metric	Comparator	Outcome	Key Finding	Clinical Implication
Ference et al. 2012	Mendelian randomization meta-analysis, n > 300,000	Genetically mediated lifelong LDL reduction	Statin-era LDL reduction	CHD incidence	Lifelong LDL lowering yields ~3× greater risk reduction per mmol/L	Timing and duration of LDL exposure are critical
Zhang et al., 2021	4 pooled cohorts, n > 18,000; 56% women	Cumulative LDL-C (AUC), time-weighted average	Most recent LDL-C	Incident CHD	Cumulative and TWA LDL independently predicted CHD; LDL slope did not	Area-under-the-curve LDL more informative than point or slope
Navar-Boggan et al., 2015	Framingham Offspring Cohort; n=1,478; free of CVD to age 55	Duration of non-HDL-C ≥160mg/dL ("years of exposure")	Single LDL/non-HDL at age 55	CHD incidence	CHD risk ↑ dose-dependently with longer exposure (HR 1.39 per decade), independent of contemporaneous lipids	Duration of exposure captures risk missed by midlife measurements
CGPS (Mortensen & Nordestgaard, 2020)	Copenhagen General Population Study; n=91,131	Single LDL-C	—	MI, ASCVD	Higher LDL associated with higher risk, amplified at older ages	Highlights limitations of single-point LDL
Nordestgaard et al., 2013; Warden et al., 2024 (FH studies)	Population screening cohorts; heterozygous FH (~1/200–1/500 prevalence)	Lifelong genetically elevated LDL-C from birth	Non-FH population (normal LDL exposure)	CHD, MI	Untreated FH associated with up to 13-fold increased CHD risk due to lifelong LDL elevation	Demonstrates extreme consequences of cumulative LDL exposure; magnitude *and* duration determine risk

Table 1. Key studies comparing cumulative LDL exposure metrics with traditional point-based lipid measurements. Summary of major studies evaluating the relationship between cumulative LDL-C metrics (e.g., cholesterol-years, area under the LDL-C curve, time-weighted averages) and cardiovascular outcomes, with comparison to traditional single-point measurements. The table highlights population characteristics, lipid metrics assessed, comparators, outcomes, key findings, and clinical implications.

From a clinical standpoint, implementation is increasingly feasible as electronic health records now capture longitudinal lipid data across multiple life stages. While early-life measurements remain sparse in many populations, even partial cumulative estimates derived from adolescence or early adulthood onward may nevertheless capture a substantial proportion of lifetime atherogenic exposure (Zheutlin et al., 2025). Such partial cumulative modeling may substantially improve risk stratification as compared with single-point assessments, particularly in populations experiencing hormonally mediated lipid shifts. As longitudinal data availability continues to expand and cumulative exposure metrics become more readily integrated into existing cardiovascular risk calculators, cholesterol-years modeling represents a practical and scalable approach to refining lifetime cardiovascular risk assessment. The clinical performance and predictive value of longitudinal risk factor integration are discussed further in the subsection *Emerging sex-specific strategies for mitigating cumulative lipid burden* below, where emerging modeling approaches demonstrate improved discrimination and reclassification beyond traditional cross-sectional tools.

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Therapeutic strategies and sex-specific limitations

Given the centrality of cumulative LDL-C exposure in atherosclerosis, therapeutic interventions aim to reduce circulating LDL-C levels, enhance clearance, or modify lipid metabolism to slow plaque progression. ~~(Table 1).~~

Therapy	Mechanism of Action	Key Efficacy Data	Notes
Statins	Inhibit HMG-CoA reductase → ↓ cholesterol synthesis → ↑ hepatic LDL receptors → ↑ LDL-C clearance	Pediatric FH: LDL-C ↓ 32% (29–35%), CIMT regression 0.01 mm, flow-mediated dilation ↑ 2.7%	Primary & secondary prevention; early initiation maximizes benefit; safe in children/adolescents
Ezetimibe	Inhibits NPC1L1 → ↓ intestinal cholesterol absorption → additive LDL-C reduction	LDL-C ↓ ~15–20% when combined with statin IMPROVE-IT: 7-year MACE 32.7% vs 34.7% (ARR 2%, HR 0.936), greater benefit in ≥75 years & diabetics	Adjunct to statin therapy, especially when target LDL-C not achieved with statins alone
PCSK9 inhibitors (Evolocumab, Alirocumab, Inclisiran)	Monoclonal antibodies or siRNA block PCSK9 → prevent LDL receptor degradation → ↑ LDL-C clearance	LDL-C ↓ 50–60% FOURIER: major CV events ↓ 15–20% ODYSSEY: LDL-C ↓ 57%, CV events ↓ 15%, safe & well-tolerated	FH, statin-intolerant, high-risk ASCVD; Inclisiran allows long-acting dosing (every 6 months)
Hormone Replacement Therapy (HRT)	Estrogen ↑ LDL receptors, ↕ HDL formation, ↑ reverse cholesterol transport (ABCA1/ABCG1)	LDL-C ↓ 0.47 mmol/L, total cholesterol ↓ 0.43 mmol/L, Lp(a) ↓ 49.46 mmol/L	Postmenopausal women; used mainly for symptomatic relief; cardiovascular benefits secondary due to risks (VTE, stroke, breast cancer)
Lipoprotein apheresis	Mechanical removal of LDL-C and Lp(a) from plasma	LDL-C & Lp(a) 55–70% per session 2-year CV event reductions: isolated LDL ↑ 54%, isolated Lp(a) ↑ 83%, combined ↑ 83.5%	Severe or treatment-resistant FH; homozygous FH; high Lp(a); resource-intensive but highly effective

Table 1. Summary of major lipid-lowering therapies, mechanisms, and clinical outcomes.

Statins remain the first-line therapy for both primary and secondary prevention of CVD. Mechanistically, statins inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis in hepatocytes (Bansal & Cassagnol, 2023). Reduced intracellular cholesterol triggers upregulation of LDL receptors on the liver surface, promoting the uptake of circulating LDL particles and lowering plasma LDL-C concentrations (Trapani et al., 2012). In children with heterozygous FH, statins have been shown to substantially reduce LDL-C levels and slow progression of atherosclerosis. A systematic review including nine randomized placebo-controlled trials (1,177 participants; median follow-up 24 weeks) found statin therapy reduced mean LDL-C by 32.15% (95% CI: 29.4–34.9%) and produced measurable improvements in brachial artery flow-mediated dilatation (2.7%

higher; 95% CI: 0.42–4.98) and carotid intima-media thickness (CIMT) (mean change 0.01 mm lower) relative to placebo, both surrogate markers of atherosclerotic burden (Vuorio et al., 2019). Adverse events, including myopathy and changes in liver enzymes, were rare and comparable to placebo, supporting the safety of early statin initiation in pediatric populations (Vuorio et al., 2019).

Ezetimibe, an adjunct to statins, inhibits the NPC1L1 transporter in the intestinal brush border, reducing absorption of dietary and biliary cholesterol (Davis & Veltri, 2007). When combined with statins, ezetimibe provides additive LDL-C reductions (~15–20%) (Hammersley & Signy, 2017). The landmark IMPROVE-IT trial randomized high-risk post-MI patients with recent acute coronary syndrome to simvastatin 40 mg versus simvastatin 40 mg plus ezetimibe 10 mg daily (median follow-up 6 years) (Cannon et al., 2015). Combination therapy further reduced LDL-C (53.7 mg/dL vs 69.5 mg/dL; $p < 0.001$) and decreased major cardiovascular events at 7 years (absolute risk reduction 2.0%; HR: 0.936; 95% CI: 0.89–0.99) (Cannon et al., 2015). Subgroup analyses indicated greater benefit for patients with diabetes (5.5% absolute risk reduction; HR: 0.86) and for older adults aged ≥75 (HR: 0.80) highlighting ezetimibe's role in high-risk populations where further LDL-C lowering is required (Giugliano et al., 2018; Cannon et al., 2015). Meta-analyses of 27 trials (>21,000 participants) confirm that statin-ezetimibe combination therapy produces superior LDL-C reduction compared to statin monotherapy (mean additional reduction 15.1%) and maintains a favourable safety profile (Morrone et al., 2012).

PCSK9 inhibitors, including monoclonal antibodies evolocumab and alirocumab, preserve LDL receptor availability by preventing PCSK9-mediated receptor degradation, significantly enhancing hepatic LDL-C clearance (Jeswani et al., 2024). Clinical trials demonstrate 50–60% LDL-C reduction in patients with heterozygous FH, and reductions in major cardiovascular events of 15–20% (Tomlinson et al., 2021). For instance, the FOURIER trial reported a 59% LDL-C reduction with evolocumab, resulting in a 15% reduction in cardiovascular events; ODYSSEY Outcomes reported a 57% LDL-C reduction with alirocumab and a 15% reduction in adverse events (Jeswani et al., 2024). Inclisiran, a long-acting small interfering RNA (siRNA) targeting PCSK9, achieves similar LDL-C reductions (>50% for 6 months) with less frequent dosing (Jeswani et al., 2024). These therapies are generally well-tolerated, with injection site reactions being the most common adverse event (Jeswani et al., 2024).

Hormone replacement therapy (HRT) in postmenopausal women can partially restore premenopausal lipid profiles (Nie et al., 2022). Postmenopausal HRT has lipid-modifying effects by upregulating LDL receptors, enhancing HDL-C formation, and stimulating reverse cholesterol transport via ABCA1/ABCG1 transporters (Nie et al., 2022). A systematic review of 73 studies found that HRT significantly reduced LDL-C by 0.47 mmol/L (95% CI: −0.55 to −0.40), total cholesterol by 0.43 mmol/L, and Lp(a) by 49.46 mg/L relative to placebo (Nie et al., 2022). Moreover, the timing of HRT initiation relative to menopause is critical to its cardiovascular effects. Observational and trial data support a "timing hypothesis," whereby initiation within ten years of menopause may confer modest cardiovascular protection, whereas later initiation may increase risks of stroke or coronary events (Hodis & Mack, 2022). Novel pharmacologic approaches, including selective estrogen receptor modulators (SERMs) and tissue-selective estrogen complexes (TSECs), aim to replicate lipid benefits while minimizing systemic risks, though large-scale cardiovascular outcome data remain limited (Pickar et al., 2018). By selectively activating estrogen receptors in hepatic and vascular tissues while sparing breast and endometrial tissue, these agents aim to preserve favourable lipid profiles and reverse cholesterol transport without increasing oncologic risk (Martinkovich et al., 2014). Integration of these therapies with statins or PCSK9 inhibitors may offer synergistic LDL-C reduction in high-risk postmenopausal women, pending further study. Although HRT improves lipid profiles, its clinical use is constrained by increased risk of venous thromboembolism, stroke, and breast cancer, so it is typically reserved for symptomatic relief, with cardiovascular benefit considered secondary (Hodis & Mack, 2022).

In patients with severe or treatment-resistant dyslipidemia, particularly FH, lipoprotein apheresis provides immediate and potent LDL-C and Lp(a) reduction (Feingold, 2023). A multicenter study by von Dryander et al. demonstrated 55–70% reduction in LDL-C and Lp(a) per session. Corresponding reductions in cardiovascular event rates over two years were 54% for patients with isolated LDL elevation, 83% for elevated Lp(a), and 83.5% for combined LDL-C and Lp(a) elevations (von Dryander et al., 2013). Apheresis is intensive and resource-demanding, but offers a life-saving intervention for patients who cannot achieve lipid targets pharmacologically (Lui et al., 2014).

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Limitations and gaps, however, remain in sex-specific and longitudinal assessment. Women remain underrepresented in clinical trials, limiting precise understanding of HRT or statin efficacy across different life stages, particularly during postmenopause (Witting et al., 2022). Longitudinal studies tracking cumulative LDL-C from childhood into adulthood remain scarce, limiting the ability to quantify lifetime exposure and optimize the timing of therapy. Despite these challenges, evidence from RCTs and observational studies consistently demonstrates that aggressive LDL-C reduction, especially when initiated early, significantly decreases the risk of cardiovascular events and mitigates cumulative lipid burden; consequently both magnitude and duration of LDL-C exposure are further confirmed to be central determinants of cardiovascular outcomes.

A summary of the discussed therapies is presented in Table 2. -

Therapy	Mechanism of Action	Key Efficacy Data	Notes
Statins	Inhibit HMG-CoA reductase → ↓ cholesterol synthesis → ↑ hepatic LDL receptors → ↑ LDL-C clearance	Pediatric FH: LDL-C ↓ 32% (29–35%), CIMT regression 0.01 mm, flow-mediated dilation ↑ 2.7%	Primary & secondary prevention; early initiation maximizes benefit; safe in children/adolescents
Ezetimibe	Inhibits NPC1L1 → ↓ intestinal cholesterol absorption → additive LDL-C reduction	LDL-C ↓ ~15–20% when combined with statin IMPROVE-IT: 7-year MACE 32.7% vs 34.7% (ARR 2%, HR 0.936), greater benefit in ≥75 years & diabetics	Adjunct to statin therapy, especially when target LDL-C not achieved with statins alone
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Hormone Replacement Therapy (HRT)	Estrogen ↑ LDL receptors, ↑ HDL formation, ↑ reverse cholesterol transport (ABCA1/ABCG1)	LDL-C ↓ 0.47 mmol/L, total cholesterol ↓ 0.43 mmol/L, Lp(a) ↓ 49.46 mmol/L	Postmenopausal women; used mainly for symptomatic relief; cardiovascular benefits secondary due to risks (VTE, stroke, breast cancer)
Lipoprotein apheresis	Mechanical removal of LDL-C and Lp(a) from plasma	LDL-C & Lp(a) 55–70% per session 2-year CV event reductions: isolated	Severe or treatment-resistant FH; homozygous FH; high Lp(a); resource-intensive but highly effective

		LDL ↑ 54%, isolated Lp(a) ↑ 83%, combined ↑ 83.5%	

Table 2. Therapeutic strategies targeting cumulative LDL-C exposure. Summary of lipid-lowering interventions, including statins, ezetimibe, PCSK9 inhibitors, hormone replacement therapy (HRT), and lipoprotein apheresis. The table highlights mechanisms of action, key efficacy data, relevant populations, and considerations.

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Emerging sex-specific strategies for mitigating cumulative lipid burden

Beyond conventional lipid-lowering therapies, emerging sex-specific strategies increasingly emphasize the timing and biological context of LDL-C exposure rather than absolute cholesterol thresholds alone. Indeed, this paradigm shift is particularly relevant for women, whose cardiovascular risk is disproportionately influenced by biological differences in lipid metabolism, hormonal transitions, and lifetime exposure trajectories.

Early trajectory-based intervention in women

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One promising approach involves the earlier identification of adverse lipid trajectories in premenopausal women, even when absolute LDL-C levels remain below traditional treatment thresholds (Roeters van Lennep et al., 2023). Women often experience prolonged periods of moderate hyperlipidemia before menopause, during which cumulative LDL-C exposure accumulates (Jeong & Kim, 2022). Incorporating trajectory-based or cholesterol-years modeling into risk assessment may therefore justify the earlier initiation of LDL-lowering therapy in select women, particularly those with additional risk modifiers such as family history, pregnancy-related dyslipidemia, or polycystic ovary syndrome (O'Kelly et al., 2022). Such strategies aim to prevent decades of unrecognized exposure that manifest as accelerated risk after menopause.

Targeting menopause as a critical inflection point

Menopause represents a biologically distinct window during which LDL-C levels rise sharply. Accordingly, emerging strategies emphasize proactive lipid monitoring and intervention during the perimenopausal transition, rather than delaying treatment until overt hypercholesterolemia or clinical events occur (Fasero & Coronado, 2025). This life-stage-specific approach aligns with cumulative risk models by prioritizing prevention at a point when lipid trajectories diverge most rapidly between sexes.

Addressing Lp(a) and genetically mediated risk

Sex-specific approaches may also be particularly relevant for Lp(a). Novel antisense oligonucleotides and siRNA therapies targeting LPA transcription offer the potential to reduce Lp(a) independently of LDL-C, addressing a component of cumulative lipid risk that is largely resistant to lifestyle modification and pharmacotherapy (Tselepis, 2023). These agents may be especially beneficial in women whose risk escalates after estrogen withdrawal makes clear genetically mediated lipid abnormalities.

Integration of cumulative lipid metrics into clinical practice

Finally, emerging strategies increasingly emphasize integration rather than new drugs alone, and evidence supports the clinical feasibility and utility of incorporating cumulative and longitudinal lipid exposure into cardiovascular risk prediction models. Traditional tools such as the Pooled Cohort Equations (PCE) rely on cross-sectional risk factor measurements and may therefore underestimate lifetime risk, particularly in individuals with prolonged moderate dyslipidemia or hormonally mediated lipid shifts (Yu et al., 2023). Recent work by Yu et al. demonstrates that integrating longitudinal risk factor data substantially improves ASCVD risk

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p[redacted] adjudicated ASCVD events, a deep learning model incorporating eight years of longitudinal risk factor data outperformed the PCE in discrimination (AUROC 0.815 vs. 0.792) and calibration, with a net reclassification index of 0.385. Notably, model inputs mirrored routinely collected clinical variables, underscoring the practicality of longitudinal implementation within existing electronic health record infrastructures. These findings provide empirical support for cumulative lipid burden modeling and suggest that risk prediction frameworks incorporating serial LDL-C exposure may more accurately capture lifetime atherogenic risk—particularly in women, whose cardiovascular risk trajectories are poorly reflected by single-point assessments. As longitudinal data capture becomes increasingly ubiquitous, integration of cumulative lipid metrics into risk calculators represents a scalable strategy to refine prevention and personalize lipid-lowering interventions across the lifespan.

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4. Conclusion

Lipid metabolism is a central determinant of CVD, with cumulative exposure to atherogenic lipoproteins—particularly LDL-C—emerging as a ~~stronger~~ more informative predictor of atherosclerotic burden than isolated midlife measurements. Epidemiological, genetic, and Mendelian-randomization studies consistently demonstrate that lifelong lower LDL-C, whether through inherited variants or early pharmacologic intervention, ~~substantially reduces coronary heart disease~~confers substantial and durable reductions in CHD risk. Sex-specific differences in lipid profiles, driven primarily by hormonal modulation, contribute to divergent CVD trajectories: men experience earlier elevations in LDL-C and greater early-life risk, whereas premenopausal women benefit from estrogen-mediated cardioprotection, which diminishes after menopause.

Importantly, empirical evidence supports the clinical relevance of assessing cumulative lipid exposure rather than relying solely on point-in-time measurements. Longitudinal analyses from the Framingham Offspring Cohort demonstrate that duration of moderate hyperlipidemia in early adulthood predicts future coronary heart disease in a dose-dependent manner, independent of contemporaneous lipid levels and traditional risk factors (Navar-Boggan et al., 2015). Notably, the majority of individuals with prolonged hyperlipidemia in early life would not have qualified for statin therapy under conventional 10-year risk-based guidelines, highlighting systematic underestimation of lifetime risk. Such findings emphasize the limitations of cross-sectional risk assessment and provide direct outcome-based support for cumulative lipid burden models.

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Advances in data availability and analytic methods further corroborate the feasibility of translating lifetime lipid assessment into clinical practice. Recent work integrating longitudinal risk factor trajectories into deep learning–based prediction models demonstrate improved discrimination and risk reclassification for ASCVD compared with traditional pooled cohort equations (Yu et al., 2023). Because these models rely on routinely collected clinical variables, including serial cholesterol measurements, they offer a scalable framework for incorporating cumulative lipid exposure into individualized risk prediction. Together, these studies suggest that longitudinal lipid assessment can meaningfully improve risk stratification, particularly in populations whose lifetime risk is inadequately captured by conventional approaches.

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Therapeutic interventions, including statins, ezetimibe, PCSK9 inhibitors, HRT, and lipoprotein apheresis, effectively target both the magnitude and duration of LDL-C exposure. Evidence highlights the importance of early initiation—particularly in high-risk populations such as children with FH—to reduce cumulative lipid burden and subsequent atherosclerotic events (van den Bosch et al., 2024). Despite such advancements, underrepresentation of women in clinical trials and limited longitudinal lipid-aging data remain key gaps, highlighting the need for sex-specific strategies and lifelong management approaches.

Collectively, these findings ~~emphasize that both the quality and duration of lipid exposure are crucial determinants of CVD risk, informing precision approaches to prevention and therapy~~.suggest a paradigm shift in cardiovascular prevention toward lifelong lipid management, emphasizing cumulative exposure rather than isolated thresholds. Incorporating longitudinal lipid trajectories into risk assessment frameworks has the

potential to refine preventive strategies and advance precision medicine approaches tailored to sex, age, and lifetime CVD risk.

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Dear Editor and Reviewer,

Thank you sincerely for all your insightful and valuable feedback, as well as for the opportunity to revise my manuscript. I appreciate the time and effort that you have invested in providing comments to improve my work. After carefully considering all comments, I have revised the manuscript accordingly. I approached the revision process with care and diligence, and I hope my responses adequately address all concerns raised.

*All page numbers are noted according to the Track Changes version of the manuscript (DOCX format).

Reviewer 1

1. Methods

> *In the Methods section, please include the total number of studies screened initially as well as the remaining number of studies included in your literature review after the exclusion criteria to give the reader more situational awareness of how many studies you are synthesizing for this topic.*

We thank the reviewer for this comment. We have updated the Methods section to include detailed PRISMA-style study selection numbers. Specifically, we screened approximately 1,000 unique records after removing duplicates and ultimately included 84 studies in the final qualitative synthesis. A PRISMA flow diagram has been added as Figure 1 (**Page 3-4**) to provide visual clarity regarding study selection and eligibility.

> **Page 3:** "The literature search yielded approximately 1,200 records across all databases. After removal of duplicates (~200), ~1000 records underwent title and abstract screening. Of these, ~850 articles were excluded based on relevance, leaving ~150 full-text articles assessed for eligibility. Following full-text review, 84 articles met inclusion criteria and were incorporated into the final qualitative synthesis.
>
> Screening, eligibility assessment, and data extraction were performed by the author. Extracted data included study design, population characteristics, lipid metrics assessed (e.g., point-based LDL-C versus cumulative measures), duration of follow-up, sex-stratified analyses, and reported cardiovascular outcomes."

2. Results

> *For the results section, consider consolidating the smaller paragraphs per section to create a few larger paragraphs that flow logically per section. Consolidation of the smaller paragraphs will aid in streamlining the main takeaways and highlighting the main points per paragraph. One example of a section to streamline and consolidate paragraphs is the "Sex-specific lipid profiles" section as there are 15 mini paragraphs total that may flow better if condensed down to 5-6 larger paragraphs with emphasized main findings.*

We agree with the reviewer that further consolidation and organization may be necessary for flow and have consolidated several smaller paragraphs throughout the review for further clarity. We have also moved the discussion of sex hormones and Lp(a) to the more relevant subheader entitled "Sex-specific lipid trajectories across the lifespan."

> *Consider adding additional transitional sentences between paragraphs to streamline the main takeaway(s) of the paragraphs in each section after consolidating smaller paragraphs together.*

Thank you for this important note. Additional transitional sentences have been added between paragraphs to guide the reader through the main takeaways.

3. Graphical figures

> *Consider adding in an additional graphical figure that describes the molecular mechanisms involved in lipid metabolism to aid in understanding potential targets for therapeutic intervention and discrepancies in sex specific outcomes.*

We thank the reviewer for this suggestion. We have added Figure 2 (**Page 5**), which presents a simplified schematic of lipid metabolism, including hepatic cholesterol synthesis, LDL receptor-mediated clearance, intestinal absorption, and reverse cholesterol transport. Key points of therapeutic intervention—statins, ezetimibe, and PCSK9 inhibitors—are indicated.

> *Consider adding in an additional graphical figure that illustrates the sex specific lipid profiles and main sex differences in CVD risk to visually highlight the main sex differences reported in the literature.*

We appreciate this recommendation and have added Figure 3 (**Page 6**), which visualizes longitudinal lipid trajectories in men and women, highlighting key inflection points such as the midlife rise in LDL-C among women during the menopausal transition. The figure also illustrates cumulative LDL exposure ("cholesterol-years") to emphasize differences in lifetime atherogenic burden.

4. Conclusion

> *Your conclusion paragraph is clear and concise but would be stronger if you added in additional sentences that discuss additional ways to address the gaps in the literature as well as positing potential therapeutics to address the sex- specific differences in CVD risk. Your second paragraph in your conclusion touches on these elements but can be made stronger with additional detailed examples to address the gaps in the literature (similar to how you wrote the last sentence of the last paragraph in the "Therapeutic strategies and sex-specific limitations" section).*

Thank you for this comment. We have revised the Conclusion to explicitly reference empirical studies demonstrating cumulative LDL-C exposure as a superior predictor of CVD risk (Navar-Boggan et al., 2015; Yu et al., 2023). We also highlight practical approaches to operationalizing cumulative risk assessment in clinical practice, including integrating longitudinal lipid measures into risk calculators, deep learning models, and sex-specific preventive strategies. Potential therapeutics are discussed as strategies to address gaps in current practice.

> **Page 15:** "Importantly, empirical evidence supports the clinical relevance of assessing cumulative lipid exposure rather than relying solely on point-in-time measurements. Longitudinal analyses from the Framingham Offspring Cohort demonstrate that duration of moderate hyperlipidemia in early adulthood predicts future coronary heart disease in a dose-dependent manner, independent of contemporaneous lipid levels and traditional risk factors (Navar-Boggan et al., 2015). Notably, the majority of individuals with prolonged hyperlipidemia in early life would not have qualified for statin therapy under conventional 10-year risk-based guidelines, highlighting systematic underestimation of lifetime risk. Such findings emphasize the limitations of cross-sectional risk assessment and provide direct outcome-based support for cumulative lipid burden models.
>
> Advances in data availability and analytic methods further corroborate the feasibility of translating lifetime lipid assessment into clinical practice. Recent work integrating longitudinal risk factor trajectories into deep learning–based prediction models demonstrate improved discrimination and risk reclassification for ASCVD compared with traditional pooled cohort equations (Yu et al., 2023). Because these models rely on routinely collected clinical variables, including serial cholesterol measurements, they offer a scalable framework for incorporating cumulative lipid exposure into individualized risk prediction. Together, these studies suggest that longitudinal lipid assessment can meaningfully improve risk stratification, particularly in populations whose lifetime risk is inadequately captured by conventional approaches."

Reviewer 2

1. Originality & significance

> *The concept of cumulative lipid burden over time is not new… the manuscript would benefit from incorporating more evidence on how this should be operationalized… additional studies or frameworks demonstrating practical methods, validated metrics, or clinical tools for evaluating long-term lipid exposure would strengthen the argument… more background regarding the gaps/errors in current methods should be discussed.*

We thank the reviewer for this thoughtful comment and agree that operationalization is essential for translational relevance. In response, we have substantially expanded the manuscript to clarify *how* cumulative lipid burden can be practically assessed using existing clinical data and emerging tools.

Specifically, we now describe multiple validated and feasible approaches for operationalizing lifelong lipid exposure, including (i) duration-above-threshold metrics (e.g., years of non-HDL-C ≥160 mg/dL), (ii) cumulative or area-under-the-curve LDL-C estimates derived from repeated measurements, and (iii) time-weighted average lipid concentrations beginning in early adulthood. These approaches are supported by longitudinal cohort studies (Navar-Boggan et al., 2015; Zhang et al., 2021; Duncan et al., 2019) demonstrating that cumulative exposure metrics predict cardiovascular outcomes independent of contemporaneous lipid levels.

> **Page 10:** “Navar-Boggan et al. provide some of the strongest longitudinal evidence that cumulative lipid exposure predicts cardiovascular outcomes more accurately than single time-point lipid measurements. Using data from the Framingham Offspring Cohort, the authors examined 1,478 adults free of cardiovascular disease through age 55 and quantified duration of moderate hyperlipidemia in early adulthood (defined as non-HDL cholesterol ≥160 mg/dL). Over a median 15-year follow-up, CHD incidence increased in a clear dose-dependent manner with longer cumulative exposure: 4.4% among individuals with no exposure, 8.1% among those with 1-10 years of exposure, and 16.5% among those with 11-20 years of exposure ($P < 0.001$) (Navar-Boggan et al., 2015). Importantly, this association persisted after adjustment for contemporaneous lipid levels at age 55 and other cardiovascular risk factors, with a 39% increase in CHD risk per decade of hyperlipidemia exposure (HR 1.39; 95% CI 1.05-1.85) (Navar-Boggan et al., 2015). Notably, 85% of participants with prolonged hyperlipidemia would not have met statin treatment thresholds under contemporary 10-year risk-based guidelines, highlighting systematic underestimation of early-life risk (Navar-Boggan et al., 2015). Even among individuals not considered statin candidates at age 55, cumulative exposure remained independently associated with future CHD (adjusted HR 1.67; 95% CI 1.06-2.64) (Navar-Boggan et al., 2015). These findings demonstrate that cumulative lipid burden captures clinically meaningful risk missed by point-in-time lipid measurements and provide direct empirical support for lifetime exposure models of atherosclerotic risk.”

To further strengthen translational relevance, we incorporated emerging clinical frameworks that leverage routinely collected electronic health record data. Notably, we now discuss Yu et al. (2023), which demonstrates that incorporation of longitudinal lipid and risk factor trajectories into a deep learning–based ASCVD risk model significantly improves discrimination and reclassification compared with the Pooled Cohort Equations, illustrating a scalable path toward clinical implementation.

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underscoring the practicality of longitudinal implementation within existing electronic health record infrastructures. These findings provide empirical support for cumulative lipid burden modeling and suggest that risk prediction frameworks incorporating serial LDL-C exposure may more accurately capture lifetime atherogenic risk—particularly in women, whose cardiovascular risk trajectories are poorly reflected by single-point assessments. As longitudinal data capture becomes increasingly ubiquitous, integration of cumulative lipid metrics into risk calculators represents a scalable strategy to refine prevention and personalize lipid-lowering interventions across the lifespan."

We also expanded discussion of the limitations of current risk assessment paradigms, including reliance on cross-sectional lipid measurements, underestimation of early-life risk, and systematic misclassification of women and younger individuals whose cumulative exposure is not captured by 10-year risk models. These gaps underscore the need for exposure-based frameworks and motivate future integration of cumulative lipid metrics into clinical risk calculators.

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We appreciate this concern and agree that explicit alignment between the stated aims and the empirical evidence is essential. In the revised Results section, we have clarified how existing longitudinal and genetic studies operationalize cumulative lipid exposure and how these findings intersect with sex-specific cardiovascular risk trajectories. While relatively few studies simultaneously quantify cumulative cholesterol and stratify outcomes by sex, we now explicitly integrate evidence from Navar-Boggan et al. (duration-based exposure), Zhang et al. (AUC and time-weighted LDL metrics), and sex-stratified trajectory data from Framingham and SWAN to demonstrate how cumulative exposure frameworks reveal differential risk accrual in men and women across the life course. We further highlight this gap as a priority area for future longitudinal research throughout the review.

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2. Introduction

> *The clinical implications of using cumulative lipid measurements to capture "lifelong cardiovascular risk" should be*

> *further clarified. Explain why assessing cumulative exposure is necessary and what current risk estimates fail to capture (e.g., missed events, misclassification, underestimation of early-life risk).*

Thank you for this thoughtful and important comment. We agree that the clinical motivation for cumulative lipid assessment required clearer articulation. In response, we substantially revised the latter half of the Introduction to explicitly address the limitations of current point-based lipid measurements and their clinical consequences. Specifically, we added a new paragraph describing how reliance on single time-point LDL-C values can underestimate early-life exposure, misclassify individuals whose cholesterol levels are lowered later through treatment, and obscure sex-specific trajectories shaped by hormonal transitions such as menopause.

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> *Please expand on the specific gap in the literature that this review intends to address. The extensive discussion of sex differences may give the impression that the topic is already well-established.*

We appreciate this observation and agree that the original framing risks obscuring the review's novelty. To address this, we revised the final paragraph of the Introduction to more clearly define the specific gap this review addresses.

> **Page 2: "**Accordingly, this literature review synthesizes current evidence to evaluate cumulative lipid exposure as a determinant of cardiovascular risk across the lifespan, with particular attention to sex-specific biology. Rather than re-establishing known sex differences in lipid profiles, this review critically examines how cumulative LDL-C burden has been measured, where empirical support exists, and where significant gaps, especially regarding sex-stratified risk estimation, persist. By integrating mechanistic insights with epidemiological data, this review aims to clarify the translational potential of cumulative lipid metrics and to identify key methodological and evidentiary barriers that must be addressed to advance sex-specific cardiovascular prevention strategies."

Rather than re-establishing known sex differences in lipid profiles, the revised manuscript now explicitly frames its contribution as a critical synthesis of cumulative lipid exposure frameworks and an evaluation of where sex-specific validation exists—and where it remains lacking. We emphasize that, despite extensive documentation of sex differences in lipid biology, few studies integrate these differences into longitudinal or cumulative lipid risk models. Identifying this gap and its translational implications constitutes a central objective of this review.

> *You state that the purpose of this review is to examine "cholesterol levels relative to age" as a proxy for cumulative lipid burden, but do not define how this index is calculated.*

Thank you for highlighting this ambiguity. We have now explicitly defined cumulative lipid burden in the Introduction as time-integrated exposure to circulating atherogenic lipoproteins.

> **Page 2:** "In this context, cumulative lipid burden may be conceptualized as the time-integrated exposure to circulating atherogenic lipoproteins, operationalized through metrics such as "cholesterol-years" or LDL years, serial aggregation of repeated lipid measurements, or genetic proxies for lifelong LDL-C elevation. However, the clinical implementation of such frameworks remains limited, and sex-specific validation is notably sparse."

We clarify that this construct is operationalized in the literature through approaches such as “cholesterol-years” or LDL-years metrics, serial aggregation of repeated lipid measurements over time, and Mendelian randomization–based proxies for lifelong LDL-C exposure. This clarification ensures that the term “cholesterol relative to age” is grounded in established, though still evolving, methodological frameworks.

> *You state that the purpose of this review is to examine “cholesterol levels relative to age” as a proxy for cumulative lipid burden, but do not define how this index is calculated.*

We agree with this concern and have revised the manuscript to ensure that all stated aims are fully supported by available evidence. Specifically, we modified the wording of the review’s aims in the Introduction to reflect that this review evaluates where sex-specific associations with cumulative lipid exposure have been empirically demonstrated and where such data remain absent.

> **Page 2: “**Accordingly, this literature review synthesizes current evidence to evaluate cumulative lipid exposure as a determinant of cardiovascular risk across the lifespan, with particular attention to sex-specific biology. Rather than re-establishing known sex differences in lipid profiles, this review critically examines how cumulative LDL-C burden has been measured, where empirical support exists, and where significant gaps, especially regarding sex-stratified risk estimation, persist. By integrating mechanistic insights with epidemiological data, this review aims to clarify the translational potential of cumulative lipid metrics and to identify key methodological and evidentiary barriers that must be addressed to advance sex-specific cardiovascular prevention strategies.”

Rather than implying the existence of comprehensive sex-stratified cumulative lipid indices, the revised manuscript now explicitly identifies the paucity of sex-specific hazard ratios and longitudinal metrics as a major gap in the literature. This reframing strengthens the internal consistency of the review and aligns its conclusions with the evidentiary status quo.

3. Methods

> *Were there additional inclusion or exclusion criteria beyond the listed search terms?*

Thank you for this suggestion. We have expanded the Methods section to clarify that additional inclusion criteria were applied beyond search terms alone. Specifically, studies were required to (i) examine human populations, (ii) report cardiovascular outcomes or atherosclerotic endpoints, and (iii) include lipid-related exposures relevant to aging or sex-specific risk. We also clarify that animal studies were excluded unless their findings had clear translational relevance to human lipid metabolism.

> **Page 3:** “Studies were selected based on predefined inclusion and exclusion criteria. Eligible studies met one or more of the following criteria: large-scale epidemiological or longitudinal cohort studies examining serum lipid levels, aging, and cardiovascular outcomes in human populations; genetic or Mendelian randomization studies evaluating lifelong exposure and cardiovascular risk; mechanistic or biochemical studies elucidating pathways by which sex hormones influence lipid metabolism and atherogenesis; and review articles synthesizing lipid metabolism and CVD risk, included to contextualize primary findings.
>
> Studies were excluded if they were non-peer-reviewed sources, case reports, editorials, or conference abstracts; focused exclusively on animal or in vitro models without clear translational relevance to human lipid metabolism; or addressed metabolic disorders unrelated to cardiovascular lipid metabolism.”

> *A more detailed summary of the number of studies screened, reviewed, and included—along with who performed the screening—would strengthen the methodology. Including a PRISMA diagram would add clarity and rigor.*

We agree and have strengthened the methodological transparency of the review accordingly. The revised Methods section now includes a detailed description of the study selection process, including the number of records identified, screened, assessed for eligibility, and included in the final synthesis, as well as clarification that screening and selection were performed by the author.

> **Page 3:** "The literature search yielded approximately 1,200 records across all databases. After removal of duplicates (~200), ~1000 records underwent title and abstract screening. Of these, ~850 articles were excluded based on relevance, leaving ~150 full-text articles assessed for eligibility. Following full-text review, 84 articles met inclusion criteria and were incorporated into the final qualitative synthesis.
>
> Screening, eligibility assessment, and data extraction were performed by the author. Extracted data included study design, population characteristics, lipid metrics assessed (e.g., point-based LDL-C versus cumulative measures), duration of follow-up, sex-stratified analyses, and reported cardiovascular outcomes."

In addition, we have added a PRISMA flow diagram (Figure 1) summarizing the literature search and screening process, in accordance with PRISMA guidelines. These additions enhance the rigor and reproducibility of the review methodology.

4. Results

> Much of the evidence on sex-based lipid differences is well-established and somewhat dated, making it unclear what new insights this review contributes. If there are recent or emerging findings, highlighting them would reinforce the novelty.

We appreciate this observation and agree that many foundational sex-based lipid differences are well established. To reinforce the novelty of this review, we revised the manuscript to reduce emphasis on re-establishing canonical differences and instead highlight recent and emerging findings. Specifically, we expanded the discussion of longitudinal cohort data linking sex-specific trajectories to cumulative exposure.

> **Pages 6-7: "**Consequently, these well-established sex differences have been reframed as divergent cumulative exposure trajectories shaped by hormonally timed inflection points rather than as static biological distinctions. Recent longitudinal analyses emphasize that cardiovascular risk divergence arises from differences in *when* and *for how long* individuals are exposed to atherogenic lipid environments, rather than from fixed sex-based lipid set points (Wilkins et al., 2024; Zheutlin et al., 2025). This temporal reframing has shifted the field away from cross-sectional lipid comparisons toward life-course modeling approaches that better capture the delayed but accelerated risk observed in postmenopausal women. Such findings highlight the need to integrate sex, age, and duration of exposure into cardiovascular risk assessment rather than treating sex differences as isolated phenomena."

> *You may wish to reduce the emphasis on re-establishing sex differences and instead focus more on summarizing new or under-discussed data.*

We agree and have revised the manuscript accordingly. Redundant explanations of sex differences—particularly estrogen-mediated lipid effects—were consolidated, and emphasis was shifted toward under-discussed longitudinal and exposure-based data. The revised Results section now prioritizes studies modeling cumulative lipid burden, early-life exposure, and sex-specific risk misclassification under current guidelines. This restructuring clarifies that sex differences are presented as modifiers of lifetime exposure rather than as standalone findings.

> *When introducing the "cholesterol-years" model, please describe how it is calculated and discuss feasibility of implementation in clinical practice.*

Thank you for this suggestion. We have clarified the “cholesterol-years” (or cumulative lipid burden) model by explicitly describing its calculation. We also added discussion of feasibility, noting that increasing availability of longitudinal electronic health records, repeated lipid testing, and integration into risk calculators makes implementation increasingly practical.

> **Page 9: “**Operationally, cumulative LDL exposure (“cholesterol-years”) is calculated by aggregating serial LDL-C measurements over time, typically as the area under the LDL-C-time curve or as a time-weighted average of repeated values across adulthood (Ference et al., 2012). In genetic studies, this exposure is approximated through lifelong LDL-C differences conferred by specific variants, providing a proxy for sustained exposure independent of treatment or behaviour (Ference et al., 2012). In observational cohorts, cumulative burden has been modeled using repeated laboratory measurements collected at regular intervals, enabling estimation of total LDL exposure across decades (Zhang et al., 2021).”
>
> **Pages 11-12:** “From a clinical standpoint, implementation is increasingly feasible as electronic health records now capture longitudinal lipid data across multiple life stages. While early-life measurements remain sparse in many populations, even partial cumulative estimates derived from adolescence or early adulthood onward may nevertheless capture a substantial proportion of lifetime atherogenic exposure. Such partial cumulative modeling may substantially improve risk stratification as compared with single-point assessments, particularly in populations experiencing hormonally mediated lipid shifts. As longitudinal data availability continues to expand and cumulative exposure metrics become more readily integrated into existing cardiovascular risk calculators, cholesterol-years modeling represents a practical and scalable approach to refining lifetime cardiovascular risk assessment.”

> *The Copenhagen example relies on single-point LDL measurements, which seems to contradict the review’s argument for cumulative LDL modeling. Using an example that incorporates cumulative LDL metrics may better support your thesis.*

We acknowledge this concern and have revised the manuscript to explicitly address this limitation. The Copenhagen General Population Study is now discussed as supportive but indirect evidence, with clear acknowledgment that its reliance on single-point LDL-C measurements limits direct assessment of cumulative exposure. We emphasized that its age-stratified risk gradients align with cumulative-burden models, underscoring the need for studies that incorporate repeated measurements. Additionally, we expanded discussion of cohorts that directly model cumulative exposure.

> **Page 10:** “Notably, the CGPS relies on single-point LDL-C measurements, which limits its ability to directly assess cumulative lipid exposure. However, its findings nevertheless align with cumulative risk models by demonstrating amplified risk at older ages, when lifetime LDL burden is greatest, but highlight the need for studies incorporating repeated measurements to more accurately quantify exposure over time.”

> *The review describes why cumulative burden makes theoretical sense but does not provide enough empirical studies demonstrating that cumulative LDL predicts outcomes better than conventional methods.*

We thank the reviewer for this important suggestion. To strengthen the empirical basis of cumulative lipid exposure models, we have added a detailed discussion of longitudinal cohort studies that directly quantify cumulative hyperlipidemia and compare its predictive value to point-in-time lipid measurements. Specifically, we added a new paragraph in the Results section describing the Framingham Offspring analysis by Navar-Boggan et al., which demonstrates a dose-dependent increase in coronary heart disease risk with longer duration of hyperlipidemia exposure, independent of lipid levels measured at age 55. This study provides direct evidence that cumulative exposure captures clinically meaningful risk missed by conventional single-measurement approaches:

Page 10: "Navar-Boggan et al. provide some of the strongest longitudinal evidence that cumulative lipid exposure predicts cardiovascular outcomes more accurately than single time-point lipid measurements. Using data from the Framingham Offspring Cohort, the authors examined 1,478 adults free of cardiovascular disease through age 55 and quantified duration of moderate hyperlipidemia in early adulthood (defined as non-HDL cholesterol ≥160 mg/dL). Over a median 15-year follow-up, CHD incidence increased in a clear dose-dependent manner with longer cumulative exposure: 4.4% among individuals with no exposure, 8.1% among those with 1-10 years of exposure, and 16.5% among those with 11-20 years of exposure ($P < 0.001$) (Navar-Boggan et al., 2015). Importantly, this association persisted after adjustment for contemporaneous lipid levels at age 55 and other cardiovascular risk factors, with a 39% increase in CHD risk per decade of hyperlipidemia exposure (HR 1.39; 95% CI 1.05-1.85) (Navar-Boggan et al., 2015). Notably, 85% of participants with prolonged hyperlipidemia would not have met statin treatment thresholds under contemporary 10-year risk-based guidelines, highlighting systematic underestimation of early-life risk (Navar-Boggan et al., 2015). Even among individuals not considered statin candidates at age 55, cumulative exposure remained independently associated with future CHD (adjusted HR 1.67; 95% CI 1.06-2.64) (Navar-Boggan et al., 2015). These findings demonstrate that cumulative lipid burden captures clinically meaningful risk missed by point-in-time lipid measurements and provide direct empirical support for lifetime exposure models of atherosclerotic risk."

> *You may consider adding more studies that directly model cumulative lipid exposure, use repeat lipid measurements, or compare cumulative vs. single LDL measurements.*

Thank you for this important suggestion. We have expanded the Results section to emphasize studies that explicitly incorporate repeated lipid measurements and duration-based exposure metrics. We also clarified the limitations of single-measurement cohorts (e.g., the Copenhagen General Population Study) and explained how their findings align with lifetime exposure models.

> *In most reviews, Table 1 summarizes the included studies. Consider adding such a table.*

We agree and have added Table 1 (**Page 11**), which summarizes key studies included in the review. This table synthesizes study design, population, lipid exposure metrics, outcome measures, and key findings, improving clarity and accessibility for readers.

> *I would consider a break down of studies by cumulative LDL vs. point-measurement since this is a main aim of your study.*

Thank you for this suggestion. Table 1 (**Page 11**) was designed to distinguish studies that use cumulative lipid exposure metrics from those that rely on single-point measurements. This distinction directly reflects the central aim of the review and helps clarify how different methodological approaches contribute to the evidence base.

> *The table summarizing lipid-lowering agents should appear after the corresponding discussion to improve flow.*

Thank you for this valuable input. We have revised the manuscript accordingly. Table 2 (**Pages 13-14**), summarizing lipid-lowering therapies, was repositioned to immediately follow the Therapeutic Implications section.

> *The section on SERMs and TSECs is compelling—are there additional novel therapeutic strategies or sex-specific approaches worth including?*

We agree with the value of this approach. Accordingly, we have added a new subsection entitled "Emerging Sex-Specific Strategies for Mitigating Cumulative Lipid Burden." This section discusses early LDL-lowering paradigms

in women, life-stage–specific responses to lipid-lowering therapies, emerging Lp(a)-targeted antisense and siRNA therapies, and sex-informed preventive strategies for conditions such as premature menopause and pregnancy-related cardiometabolic complications. These additions extend beyond SERMs/TSECs and highlight future directions for reducing lifetime lipid exposure in women in the Therapeutic Implications subsection.

> *You may consider some subheadings within the results section to assist with the flow.*

We agree and have added subheadings within the Results section to improve organization and guide the reader through key themes, particularly in the section addressing therapies.

> *Sex-differences including estrogen's effects are explained several times; consider consolidating and focusing more on lifelong exposure and novel treatments.*

We appreciate this suggestion and have consolidated discussions of estrogen-mediated lipid effects on sex differences and CVD into a single section under "Sex-specific lipid trajectories across the lifespan." Redundant explanations were removed, allowing greater emphasis on lifelong lipid exposure, cumulative risk modeling, and novel therapeutic approaches.

5. Conclusion

> *Please elaborate on the clinical implications. Should clinicians be assessing lifetime lipid exposure rather than relying solely on point measurements? If so, what practical methods exist?*

Thank you for this insightful comment. We have expanded the conclusion and clinical practice integration sections to more explicitly address translational implications. Specifically, we clarify that cumulative LDL exposure ("cholesterol-years") provides clinically meaningful risk information beyond single-point lipid measurements and should be considered as a complementary framework rather than a replacement for current practice.

> **Page 15:** "Advances in data availability and analytic methods further corroborate the feasibility of translating lifetime lipid assessment into clinical practice. Recent work integrating longitudinal risk factor trajectories into deep learning–based prediction models demonstrate improved discrimination and risk reclassification for ASCVD compared with traditional pooled cohort equations (Yu et al., 2023). Because these models rely on routinely collected clinical variables, including serial cholesterol measurements, they offer a scalable framework for incorporating cumulative lipid exposure into individualized risk prediction. Together, these studies suggest that longitudinal lipid assessment can meaningfully improve risk stratification, particularly in populations whose lifetime risk is inadequately captured by conventional approaches."

> *Are there studies that demonstrate how cumulative LDL assessment improves risk stratification or outcomes? Including these would strengthen the translational relevance of your conclusions.*

We agree and have incorporated longitudinal and modeling studies demonstrating improved risk stratification using cumulative exposure both in the Results section and in the Conclusion. These include Navar-Boggan et al. (2015), which showed a dose-dependent increase in coronary heart disease risk with longer duration of moderate hyperlipidemia independent of contemporaneous lipid levels, and Yu et al. (2023), which demonstrated that incorporation of longitudinal lipid trajectories using deep learning significantly improved ASCVD risk discrimination and reclassification compared with the Pooled Cohort Equations.

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predicts future coronary heart disease in a dose-dependent manner, independent of contemporaneous lipid levels and traditional risk factors (Navar-Boggan et al., 2015). Notably, the majority of individuals with prolonged hyperlipidemia in early life would not have qualified for statin therapy under conventional 10-year risk-based guidelines, highlighting systematic underestimation of lifetime risk. Such findings emphasize the limitations of cross-sectional risk assessment and provide direct outcome-based support for cumulative lipid burden models.”

Dear Editor and Reviewer,

Thank you sincerely for all your insightful and valuable feedback, as well as for the opportunity to revise my manuscript. I appreciate the time and effort that you have invested in providing comments to improve my work. After carefully considering all comments, I have revised the manuscript accordingly. I approached the revision process with care and diligence, and I hope my responses adequately address all concerns raised.

*All page numbers are noted according to the Track Changes version of the manuscript (DOCX format).

Reviewer 2

1. Originality & significance

> *The concept of cumulative lipid burden over time is not new… the manuscript would benefit from incorporating more evidence on how this should be operationalized… additional studies or frameworks demonstrating practical methods, validated metrics, or clinical tools for evaluating long-term lipid exposure would strengthen the argument… more background regarding the gaps/errors in current methods should be discussed.*

We thank the reviewer for this thoughtful comment and agree that operationalization is essential for translational relevance. In response, we have substantially expanded the manuscript to clarify *how* cumulative lipid burden can be practically assessed using existing clinical data and emerging tools.

Specifically, we now describe multiple validated and feasible approaches for operationalizing lifelong lipid exposure, including (i) duration-above-threshold metrics (e.g., years of non-HDL-C ≥160 mg/dL), (ii) cumulative or area-under-the-curve LDL-C estimates derived from repeated measurements, and (iii) time-weighted average lipid concentrations beginning in early adulthood. These approaches are supported by longitudinal cohort studies (Navar-Boggan et al., 2015; Zhang et al., 2021; Duncan et al., 2019) demonstrating that cumulative exposure metrics predict cardiovascular outcomes independent of contemporaneous lipid levels.

> **Page 10:** “Navar-Boggan et al. provide some of the strongest longitudinal evidence that cumulative lipid exposure predicts cardiovascular outcomes more accurately than single time-point lipid measurements. Using data from the Framingham Offspring Cohort, the authors examined 1,478 adults free of cardiovascular disease through age 55 and quantified duration of moderate hyperlipidemia in early adulthood (defined as non-HDL cholesterol ≥160 mg/dL). Over a median 15-year follow-up, CHD incidence increased in a clear dose-dependent manner with longer cumulative exposure: 4.4% among individuals with no exposure, 8.1% among those with 1-10 years of exposure, and 16.5% among those with 11-20 years of exposure ($P < 0.001$) (Navar-Boggan et al., 2015). Importantly, this association persisted after adjustment for contemporaneous lipid levels at age 55 and other cardiovascular risk factors, with a 39% increase in CHD risk per decade of hyperlipidemia exposure (HR 1.39; 95% CI 1.05-1.85) (Navar-Boggan et al., 2015). Notably, 85% of participants with prolonged hyperlipidemia would not have met statin treatment thresholds under contemporary 10-year risk-based guidelines, highlighting systematic underestimation of early-life risk (Navar-Boggan et al., 2015). Even among individuals not considered statin candidates at age 55, cumulative exposure remained independently associated with future CHD (adjusted HR 1.67; 95% CI 1.06-2.64) (Navar-Boggan et al., 2015). These findings demonstrate that cumulative lipid burden captures clinically meaningful risk missed by point-in-time lipid measurements and provide direct empirical support for lifetime exposure models of atherosclerotic risk.”

To further strengthen translational relevance, we incorporated emerging clinical frameworks that leverage routinely collected electronic health record data. Notably, we now discuss Yu et al. (2023), which demonstrates that incorporation of longitudinal lipid and risk factor trajectories into a deep learning–based ASCVD risk model significantly improves discrimination and reclassification compared with the Pooled Cohort Equations, illustrating a scalable path toward clinical implementation.

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We also expanded discussion of the limitations of current risk assessment paradigms, including reliance on cross-sectional lipid measurements, underestimation of early-life risk, and systematic misclassification of women and younger individuals whose cumulative exposure is not captured by 10-year risk models. These gaps underscore the need for exposure-based frameworks and motivate future integration of cumulative lipid metrics into clinical risk calculators.

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2. Introduction

> *The clinical implications of using cumulative lipid measurements to capture “lifelong cardiovascular risk” should be further clarified. Explain why assessing cumulative exposure is necessary and what current risk estimates fail to capture (e.g., missed events, misclassification, underestimation of early-life risk).*

Thank you for this thoughtful and important comment. We agree that the clinical motivation for cumulative lipid assessment required clearer articulation. In response, we substantially revised the latter half of the Introduction to explicitly address the limitations of current point-based lipid measurements and their clinical consequences. Specifically, we added a new paragraph describing how reliance on single time-point LDL-C values can underestimate early-life exposure, misclassify individuals whose cholesterol levels are lowered later through treatment, and obscure sex-specific trajectories shaped by hormonal transitions such as menopause.

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Rather than re-establishing known sex differences in lipid profiles, the revised manuscript now explicitly frames its contribution as a critical synthesis of cumulative lipid exposure frameworks and an evaluation of where sex-specific validation exists—and where it remains lacking. We emphasize that, despite extensive documentation of sex differences in lipid biology, few studies integrate these differences into longitudinal or cumulative lipid risk models. Identifying this gap and its translational implications constitutes a central objective of this review.

> *You state that the purpose of this review is to examine “cholesterol levels relative to age” as a proxy for cumulative lipid burden, but do not define how this index is calculated.*

Thank you for highlighting this ambiguity. We have now explicitly defined cumulative lipid burden in the Introduction as time-integrated exposure to circulating atherogenic lipoproteins.

> **Page 2:** “In this context, cumulative lipid burden may be conceptualized as the time-integrated exposure to circulating atherogenic lipoproteins, operationalized through metrics such as “cholesterol-years” or LDL years, serial aggregation of repeated lipid measurements, or genetic proxies for lifelong LDL-C elevation. However, the clinical implementation of such frameworks remains limited, and sex-specific validation is notably sparse.”

We clarify that this construct is operationalized in the literature through approaches such as “cholesterol-years” or LDL-years metrics, serial aggregation of repeated lipid measurements over time, and Mendelian randomization–based proxies for lifelong LDL-C exposure. This clarification ensures that the term “cholesterol relative to age” is grounded in established, though still evolving, methodological frameworks.

> *You state that the purpose of this review is to examine “cholesterol levels relative to age” as a proxy for cumulative lipid burden, but do not define how this index is calculated.*

We agree with this concern and have revised the manuscript to ensure that all stated aims are fully supported by available evidence. Specifically, we modified the wording of the review’s aims in the Introduction to reflect that this review evaluates where sex-specific associations with cumulative lipid exposure have been empirically demonstrated and where such data remain absent.

> **Page 2: “**Accordingly, this literature review synthesizes current evidence to evaluate cumulative lipid exposure as a determinant of cardiovascular risk across the lifespan, with particular attention to sex-specific biology. Rather than re-establishing known sex differences in lipid profiles, this review critically examines how cumulative LDL-C burden has been measured, where empirical support exists, and where significant gaps, especially regarding sex-stratified risk estimation, persist. By integrating mechanistic insights with epidemiological data, this review aims to clarify the translational potential of cumulative lipid metrics and to identify key methodological and evidentiary barriers that must be addressed to advance sex-specific cardiovascular prevention strategies.”

Rather than implying the existence of comprehensive sex-stratified cumulative lipid indices, the revised manuscript now explicitly identifies the paucity of sex-specific hazard ratios and longitudinal metrics as a major gap in the literature. This reframing strengthens the internal consistency of the review and aligns its conclusions with the evidentiary status quo.

3. Methods

> *Were there additional inclusion or exclusion criteria beyond the listed search terms?*

Thank you for this suggestion. We have expanded the Methods section to clarify that additional inclusion criteria were applied beyond search terms alone. Specifically, studies were required to (i) examine human populations, (ii) report cardiovascular outcomes or atherosclerotic endpoints, and (iii) include lipid-related exposures relevant to aging or sex-specific risk. We also clarify that animal studies were excluded unless their findings had clear translational relevance to human lipid metabolism.

> **Page 3:** “Studies were selected based on predefined inclusion and exclusion criteria. Eligible studies met one or more of the following criteria: large-scale epidemiological or longitudinal cohort studies examining serum lipid levels, aging, and cardiovascular outcomes in human populations; genetic or Mendelian randomization studies evaluating lifelong exposure and cardiovascular risk; mechanistic or biochemical

studies elucidating pathways by which sex hormones influence lipid metabolism and atherogenesis; and review articles synthesizing lipid metabolism and CVD risk, included to contextualize primary findings.

Studies were excluded if they were non-peer-reviewed sources, case reports, editorials, or conference abstracts; focused exclusively on animal or in vitro models without clear translational relevance to human lipid metabolism; or addressed metabolic disorders unrelated to cardiovascular lipid metabolism."

> *A more detailed summary of the number of studies screened, reviewed, and included—along with who performed the screening—would strengthen the methodology. Including a PRISMA diagram would add clarity and rigor.*

We agree and have strengthened the methodological transparency of the review accordingly. The revised Methods section now includes a detailed description of the study selection process, including the number of records identified, screened, assessed for eligibility, and included in the final synthesis, as well as clarification that screening and selection were performed by the author.

> **Page 3:** "The literature search yielded approximately 1,200 records across all databases. After removal of duplicates (~200), ~1000 records underwent title and abstract screening. Of these, ~850 articles were excluded based on relevance, leaving ~150 full-text articles assessed for eligibility. Following full-text review, 84 articles met inclusion criteria and were incorporated into the final qualitative synthesis.
>
> Screening, eligibility assessment, and data extraction were performed by the author. Extracted data included study design, population characteristics, lipid metrics assessed (e.g., point-based LDL-C versus cumulative measures), duration of follow-up, sex-stratified analyses, and reported cardiovascular outcomes."

In addition, we have added a PRISMA flow diagram (Figure 1) summarizing the literature search and screening process, in accordance with PRISMA guidelines. These additions enhance the rigor and reproducibility of the review methodology.

4. Results

> Much of the evidence on sex-based lipid differences is well-established and somewhat dated, making it unclear what new insights this review contributes. If there are recent or emerging findings, highlighting them would reinforce the novelty.

We appreciate this observation and agree that many foundational sex-based lipid differences are well established. To reinforce the novelty of this review, we revised the manuscript to reduce emphasis on re-establishing canonical differences and instead highlight recent and emerging findings. Specifically, we expanded the discussion of longitudinal cohort data linking sex-specific trajectories to cumulative exposure.

> **Pages 6-7: "**Consequently, these well-established sex differences have been reframed as divergent cumulative exposure trajectories shaped by hormonally timed inflection points rather than as static biological distinctions. Recent longitudinal analyses emphasize that cardiovascular risk divergence arises from differences in *when* and *for how long* individuals are exposed to atherogenic lipid environments, rather than from fixed sex-based lipid set points (Wilkins et al., 2024; Zheutlin et al., 2025). This temporal reframing has shifted the field away from cross-sectional lipid comparisons toward life-course modeling approaches that better capture the delayed but accelerated risk observed in postmenopausal women. Such findings highlight the need to integrate sex, age, and duration of exposure into cardiovascular risk assessment rather than treating sex differences as isolated phenomena."

> *You may wish to reduce the emphasis on re-establishing sex differences and instead focus more on summarizing new or under-discussed data.*

We agree and have revised the manuscript accordingly. Redundant explanations of sex differences—particularly estrogen-mediated lipid effects—were consolidated, and emphasis was shifted toward under-discussed longitudinal and exposure-based data. The revised Results section now prioritizes studies modeling cumulative lipid burden, early-life exposure, and sex-specific risk misclassification under current guidelines. This restructuring clarifies that sex differences are presented as modifiers of lifetime exposure rather than as standalone findings.

> *When introducing the "cholesterol-years" model, please describe how it is calculated and discuss feasibility of implementation in clinical practice.*

Thank you for this suggestion. We have clarified the "cholesterol-years" (or cumulative lipid burden) model by explicitly describing its calculation. We also added discussion of feasibility, noting that increasing availability of longitudinal electronic health records, repeated lipid testing, and integration into risk calculators makes implementation increasingly practical.

> **Page 9: "**Operationally, cumulative LDL exposure ("cholesterol-years") is calculated by aggregating serial LDL-C measurements over time, typically as the area under the LDL-C-time curve or as a time-weighted average of repeated values across adulthood (Ference et al., 2012). In genetic studies, this exposure is approximated through lifelong LDL-C differences conferred by specific variants, providing a proxy for sustained exposure independent of treatment or behaviour (Ference et al., 2012). In observational cohorts, cumulative burden has been modeled using repeated laboratory measurements collected at regular intervals, enabling estimation of total LDL exposure across decades (Zhang et al., 2021)."
>
> **Pages 11-12:** "From a clinical standpoint, implementation is increasingly feasible as electronic health records now capture longitudinal lipid data across multiple life stages. While early-life measurements remain sparse in many populations, even partial cumulative estimates derived from adolescence or early adulthood onward may nevertheless capture a substantial proportion of lifetime atherogenic exposure. Such partial cumulative modeling may substantially improve risk stratification as compared with single-point assessments, particularly in populations experiencing hormonally mediated lipid shifts. As longitudinal data availability continues to expand and cumulative exposure metrics become more readily integrated into existing cardiovascular risk calculators, cholesterol-years modeling represents a practical and scalable approach to refining lifetime cardiovascular risk assessment."

> *The Copenhagen example relies on single-point LDL measurements, which seems to contradict the review's argument for cumulative LDL modeling. Using an example that incorporates cumulative LDL metrics may better support your thesis.*

We acknowledge this concern and have revised the manuscript to explicitly address this limitation. The Copenhagen General Population Study is now discussed as supportive but indirect evidence, with clear acknowledgment that its reliance on single-point LDL-C measurements limits direct assessment of cumulative exposure. We emphasized that its age-stratified risk gradients align with cumulative-burden models, underscoring the need for studies that incorporate repeated measurements. Additionally, we expanded discussion of cohorts that directly model cumulative exposure.

> **Page 10:** "Notably, the CGPS relies on single-point LDL-C measurements, which limits its ability to directly assess cumulative lipid exposure. However, its findings nevertheless align with cumulative risk models by demonstrating amplified risk at older ages, when lifetime LDL burden is greatest, but highlight the need for studies incorporating repeated measurements to more accurately quantify exposure over time."

> *The review describes why cumulative burden makes theoretical sense but does not provide enough empirical studies demonstrating that cumulative LDL predicts outcomes better than conventional methods.*

We thank the reviewer for this important suggestion. To strengthen the empirical basis of cumulative lipid exposure models, we have added a detailed discussion of longitudinal cohort studies that directly quantify cumulative hyperlipidemia and compare its predictive value to point-in-time lipid measurements. Specifically, we added a new paragraph in the Results section describing the Framingham Offspring analysis by Navar-Boggan et al., which demonstrates a dose-dependent increase in coronary heart disease risk with longer duration of hyperlipidemia exposure, independent of lipid levels measured at age 55. This study provides direct evidence that cumulative exposure captures clinically meaningful risk missed by conventional single-measurement approaches:

> **Page 10: "**Navar-Boggan et al. provide some of the strongest longitudinal evidence that cumulative lipid exposure predicts cardiovascular outcomes more accurately than single time-point lipid measurements. Using data from the Framingham Offspring Cohort, the authors examined 1,478 adults free of cardiovascular disease through age 55 and quantified duration of moderate hyperlipidemia in early adulthood (defined as non-HDL cholesterol ≥160 mg/dL). Over a median 15-year follow-up, CHD incidence increased in a clear dose-dependent manner with longer cumulative exposure: 4.4% among individuals with no exposure, 8.1% among those with 1-10 years of exposure, and 16.5% among those with 11-20 years of exposure ($P < 0.001$) (Navar-Boggan et al., 2015). Importantly, this association persisted after adjustment for contemporaneous lipid levels at age 55 and other cardiovascular risk factors, with a 39% increase in CHD risk per decade of hyperlipidemia exposure (HR 1.39; 95% CI 1.05-1.85) (Navar-Boggan et al., 2015). Notably, 85% of participants with prolonged hyperlipidemia would not have met statin treatment thresholds under contemporary 10-year risk-based guidelines, highlighting systematic underestimation of early-life risk (Navar-Boggan et al., 2015). Even among individuals not considered statin candidates at age 55, cumulative exposure remained independently associated with future CHD (adjusted HR 1.67; 95% CI 1.06-2.64) (Navar-Boggan et al., 2015). These findings demonstrate that cumulative lipid burden captures clinically meaningful risk missed by point-in-time lipid measurements and provide direct empirical support for lifetime exposure models of atherosclerotic risk."

> *You may consider adding more studies that directly model cumulative lipid exposure, use repeat lipid measurements, or compare cumulative vs. single LDL measurements.*

Thank you for this important suggestion. We have expanded the Results section to emphasize studies that explicitly incorporate repeated lipid measurements and duration-based exposure metrics. We also clarified the limitations of single-measurement cohorts (e.g., the Copenhagen General Population Study) and explained how their findings align with lifetime exposure models.

> *In most reviews, Table 1 summarizes the included studies. Consider adding such a table.*

We agree and have added Table 1 (**Page 11**), which summarizes key studies included in the review. This table synthesizes study design, population, lipid exposure metrics, outcome measures, and key findings, improving clarity and accessibility for readers.

> *I would consider a break down of studies by cumulative LDL vs. point-measurement since this is a main aim of your study.*

Thank you for this suggestion. Table 1 (**Page 11**) was designed to distinguish studies that use cumulative lipid exposure metrics from those that rely on single-point measurements. This distinction directly reflects the central aim of the review and helps clarify how different methodological approaches contribute to the evidence base.

> *The table summarizing lipid-lowering agents should appear after the corresponding discussion to improve flow.*

Thank you for this valuable input. We have revised the manuscript accordingly. Table 2 (**Pages 13-14**), summarizing lipid-lowering therapies, was repositioned to immediately follow the Therapeutic Implications section.

> *The section on SERMs and TSECs is compelling—are there additional novel therapeutic strategies or sex-specific approaches worth including?*

We agree with the value of this approach. Accordingly, we have added a new subsection entitled “Emerging Sex-Specific Strategies for Mitigating Cumulative Lipid Burden.” This section discusses early LDL-lowering paradigms in women, life-stage–specific responses to lipid-lowering therapies, emerging Lp(a)-targeted antisense and siRNA therapies, and sex-informed preventive strategies for conditions such as premature menopause and pregnancy-related cardiometabolic complications. These additions extend beyond SERMs/TSECs and highlight future directions for reducing lifetime lipid exposure in women in the Therapeutic Implications subsection.

> *You may consider some subheadings within the results section to assist with the flow.*

We agree and have added subheadings within the Results section to improve organization and guide the reader through key themes, particularly in the section addressing therapies.

> *Sex-differences including estrogen’s effects are explained several times; consider consolidating and focusing more on lifelong exposure and novel treatments.*

We appreciate this suggestion and have consolidated discussions of estrogen-mediated lipid effects on sex differences and CVD into a single section under “Sex-specific lipid trajectories across the lifespan.” Redundant explanations were removed, allowing greater emphasis on lifelong lipid exposure, cumulative risk modeling, and novel therapeutic approaches.

5. Conclusion

> *Please elaborate on the clinical implications. Should clinicians be assessing lifetime lipid exposure rather than relying solely on point measurements? If so, what practical methods exist?*

Thank you for this insightful comment. We have expanded the conclusion and clinical practice integration sections to more explicitly address translational implications. Specifically, we clarify that cumulative LDL exposure (“cholesterol-years”) provides clinically meaningful risk information beyond single-point lipid measurements and should be considered as a complementary framework rather than a replacement for current practice.

> **Page 15:** “Advances in data availability and analytic methods further corroborate the feasibility of translating lifetime lipid assessment into clinical practice. Recent work integrating longitudinal risk factor trajectories into deep learning–based prediction models demonstrate improved discrimination and risk reclassification for ASCVD compared with traditional pooled cohort equations (Yu et al., 2023). Because these models rely on routinely collected clinical variables, including serial cholesterol measurements, they offer a scalable framework for incorporating cumulative lipid exposure into individualized risk prediction. Together, these studies suggest that longitudinal lipid assessment can meaningfully improve risk stratification, particularly in populations whose lifetime risk is inadequately captured by conventional approaches.”

> *Are there studies that demonstrate how cumulative LDL assessment improves risk stratification or outcomes? Including these would strengthen the translational relevance of your conclusions.*

We agree and have incorporated longitudinal and modeling studies demonstrating improved risk stratification using cumulative exposure both in the Results section and in the Conclusion. These include Navar-Boggan et al. (2015), which showed a dose-dependent increase in coronary heart disease risk with longer duration of moderate hyperlipidemia independent of contemporaneous lipid levels, and Yu et al. (2023), which demonstrated that incorporation of longitudinal lipid trajectories using deep learning significantly improved ASCVD risk discrimination and reclassification compared with the Pooled Cohort Equations.

> **Page 15:** “Importantly, empirical evidence supports the clinical relevance of assessing cumulative lipid exposure rather than relying solely on point-in-time measurements. Longitudinal analyses from the Framingham Offspring Cohort demonstrate that duration of moderate hyperlipidemia in early adulthood predicts future coronary heart disease in a dose-dependent manner, independent of contemporaneous lipid levels and traditional risk factors (Navar-Boggan et al., 2015). Notably, the majority of individuals with prolonged hyperlipidemia in early life would not have qualified for statin therapy under conventional 10-year risk-based guidelines, highlighting systematic underestimation of lifetime risk. Such findings emphasize the limitations of cross-sectional risk assessment and provide direct outcome-based support for cumulative lipid burden models.”

1/15/2026

Submission 100125, *"Unfavourable Curves: Sex-Specific Lipid Metabolism and Lifelong Cardiovascular Risk"*

Post-Revision Critical Review (with positive and critical feedback):

- The text additions to the introduction enhance the goals of the manuscript and logically flow well to lead into the Method and Results sections.
- The addition of paragraphs highlighting the importance of metrics to indicate lifelong cardiovascular risk assessment with a focus on sex-specific biology strengthens the manuscript.
- In the literature strategy section of the Methods, please add in a clarifying sentence that states the date range of studies searched for during the literature search.
- The sentence "The search encompassed publications available in English up to October 2025." should include more detail such as the earliest date used or a statement clarifying the time window with more information on the early date criteria used in your search.
- The search terms paragraph does a great job delineating the search terms in enough detail for replication. However, I would recommend adding more detail similar to the search terms paragraph to the previous paragraph under literature search strategy to enhance the rigor of the Methods.
- In the inclusion and exclusion criteria section, the second paragraph first sentence should be edited to read "Studies were excluded if they were not **from** non-peer reviewed…".
- Figure 1 is clear and describes the method workflow well. The addition of Figure 2 describing the molecular pathways involved in lipid metabolism aids in contextualizing the review findings. However, the figure legend for Figure 3 currently states "Figure 2." Please update to reflect that this legend is for Figure 3.
- Text edits to the Results sections make the overall findings easier to interpret with an emphasis on the manuscript's narrative, which strengthens the overall review.
- In the fourth paragraph of the empirical support for the cholesterol-years model subsection of the results, please add the year in parentheses to read Ferrence et al. (2012) for all references to Ferrence et al. when not referencing the study at the end of the sentence.
- Please read through the results sections and add the year in parentheses after any et al. references that are not at the end of the sentences.

- Please edit the first sentence that references Table 1 in the text to convey what is in the table (specifically “Table 1 synthesizes key studies comparing **hookup (?)** between cumulative LDL metrics…”).
- The additions of Tables 1 and 2 synthesize the results discussed in each respective section well.
- The Conclusion section is written clearly and concisely to end the manuscript on an impactful note that highlights the importance of shifting the CVD prevention paradigm to promote enhanced risk assessment and therapeutic intervention to decrease the gap between sexes in identifying lifelong CVD risk.

Final Decision: Accept with minor revisions